



Published in final edited form as:

J Transl Gastroenterol. 2024 June ; 2(2): 125–130. doi:10.14218/JTG.2024.00017.

Epigenomics and the Brain-gut Axis: Impact of Adverse Childhood Experiences and Therapeutic Challenges

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Abstract

The brain-gut axis represents a bidirectional communication network that integrates neural, hormonal, and immunological signaling between the central nervous system and the gastrointestinal tract. Adverse childhood experiences (ACEs) have increasingly been recognized for their profound impact on this axis, with implications for both mental and physical health outcomes. This mini-review explores the emerging field of epigenomics—specifically, how epigenetic modifications incurred by ACEs can influence the brain-gut axis and contribute to the pathophysiology of various disorders. We examine the evidence linking epigenetic mechanisms such as DNA methylation, histone modifications, and non-coding RNAs to the modulation of gene expression involved in stress responses, neurodevelopment, and immune function—all of which intersect at the brain-gut axis. Additionally, we discuss the emerging potential of the gut microbiome as both a target and mediator of epigenetic changes, further influencing brain-gut communication in the context of ACEs. The methodological and therapeutic challenges posed by these insights are significant. The reversibility of epigenetic marks and the long-term consequences of early life stress require innovative and comprehensive approaches to intervention. This underscores the need for comprehensive strategies encompassing psychosocial, pharmacological, neuromodulation, and lifestyle interventions tailored to address ACEs' individualized and persistent effects. Future directions call for a multi-disciplinary approach and longitudinal studies to uncover the full extent of ACEs' impact on epigenetic regulation and the brain-gut axis, with the goal of developing targeted therapies to mitigate the long-lasting effects on health.

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Author contributions

JWW and GAH contributed equally to the intellectual content and drafting of the manuscript.

Conflict of interest

JWW has been a member of the JTJG editorial board since 2023. GAH has been Vice President of Pharmacogenomic Science at Phenomics Health, Inc. since 2023. The authors have no other conflict of interests related to this publication.

Keywords

Epigenomics; Brain-gut axis; Adverse childhood events; Chronic stress; Functional bowel disorders; Mental health disorders

Introduction

Epigenomics provides transformative insights into the dynamic interplay between genetics and the environment. An intriguing aspect of epigenomic research is its implications for the brain-gut axis, defined as the bidirectional communication pathway that links the gut and central nervous systems. This includes neuroendocrine, paracrine, and immune system pathways, intestinal barrier integrity, vagal and primary sensory pathways, and the emerging role of the microbiome in modulating these pathways. This relationship implicates a variety of physiological and pathological states, particularly psychiatric and gastrointestinal disorders. Recent studies reveal that epigenomic modifications serve as critical modulators of brain and gut function, offering fertile ground for translational applications. Recent reviews address the role of epigenomics in several clinically significant disorders of the brain-gut axis, including neurodegenerative disorders, depression, visceral pain, and the evolving role of the microbiome.^{1–4} In this mini review, we focus on areas we believe merit serious attention as this field of research moves forward, specifically the role of epigenomic-mediated changes following adverse childhood experiences (ACEs) and their implications for disorders involving the brain-gut axis later in life. We also discuss emerging therapeutic applications involving neuromodulation to potentially mitigate the risk of developing disorders of the brain-gut axis and manage gastrointestinal (GI) symptoms. Unsurprisingly, ACEs have a profound economic impact on future healthcare burdens.⁵

Epigenomics refers to the study of heritable changes in gene expression that do not involve changes to the underlying DNA sequence, a change in phenotype without a change in genotype.⁶ These changes may last through cell divisions for the remainder of the cell's life and multiple generations. Epigenomic mechanisms include DNA methylation, histone modifications, non-coding RNA (ncRNA), and variable noncoding *cis*- and *trans*-regulators of gene expression. Epigenomic processes are fundamental in shaping the development of the nervous system, where they influence gene expression involved in neural proliferation, differentiation, and synaptic plasticity.⁷ In the gut, epigenomic mechanisms regulate gut development, modulate the immune response, maintain gut barrier integrity, and influence the composition and function of the gut microbiome.⁸

The individual differences in the expression and function of epigenomic regulatory pathways underlie the heterogeneity observed in disease risk and differential responses to therapeutic interventions (Table 1).^{9–11}

Epigenomics and adverse childhood experiences

The interplay between epigenomics, the brain-gut axis, and ACEs presents a profound study area with significant implications for health across the lifespan. ACEs are one of the most robust predictors of psychiatric diseases such as major depressive disorder

(MDD) throughout the human lifespan⁸ and across generations.¹² The transgenerational transmission of the risk of psychiatric disorders is mediated by genetic variation and epigenomic modifications. There is also evidence that socioeconomic status, as inferred from geographic locale apart from ancestry, can directly impact the results of significant polygenic variants from genome-wide association studies (GWAS) of complex traits.¹³ The mechanisms involved are poorly understood. Estimates of the heritability of MDD from twin studies vary but typically range from 40% to 50%.¹⁴ This indicates that about half of the risk of developing MDD is due to genetics, with the remainder attributable to environmental/experiential factors.¹⁵

ACEs, which encompass a range of stressful environmental experiences during childhood, have been shown to have lasting impacts on physical and psychological well-being. Epigenomic mechanisms provide potent insights into how such early adversities can lead to long-term changes in gene expression, potentially influencing the development and function of the brain-gut axis.¹⁶

Large population studies, such as UK Biobank, have confirmed the results of earlier studies that demonstrated highly significant associations between psychiatric disorders and gastrointestinal disorders following ACE. For example, in an analysis of the Netherlands Mental Health Survey, respondents with a history of ACE ($N = 4,054$) suffered significantly more often from digestive disorders (OR: 1.89–2.95) than from any other somatic disease state.¹⁷ Meta-analyses of irritable bowel syndrome showed that one-third of patients had a comorbid diagnosis of generalized anxiety disorder, and one-quarter had a diagnosis of MDD.¹⁸ Multiple GWAS have demonstrated shared genetic architecture between inflammatory bowel disease and anxiety and depression.^{19,20} A GWAS of peptic ulcer disease showed a significant association with depression in addition to infection by *H. Pylori*.²¹

Trauma experienced in early life can disrupt the regulation of the hypothalamic-pituitary-adrenal (HPA) axis, which is crucial for stress response modulation. Epigenomic alterations, particularly in genes related to the HPA axis, such as the glucocorticoid receptor gene (*NR3C1*), have been observed in response to early life stress.²² These modifications may produce long-term changes in the way individuals respond to stress and can influence susceptibility to various disorders, including those associated with the brain-gut axis, such as irritable bowel syndrome (IBS). In summary, stress can significantly affect GI function. During critical developmental windows, the gut is susceptible to stress-related neuroendocrine and immune modifications resulting from altered epigenomic programming. Early life stress is associated with changes in gut motility, barrier function, and the gut microbiome, all of which can have lasting effects on GI health and contribute to the pathogenesis of GI disorders.

The gut microbiome is established after delivery in early life, a process in which stress can interfere. Epigenomic modifications may alter host-microbiome interactions or vice versa, influencing the composition and function of the gut microbiota and potentially affecting the individual's stress reactivity profile.²³ Dysfunctional microbiota-brain-gut interactions have been hypothesized to contribute to various diseases, including psychiatric disorders such

as anxiety and depression.²⁴ Most studies focusing on the role of the microbiome and brain-gut disorders have been descriptive and report statistically significant correlations. Future studies must include mechanistically focused experimental designs that address the causality or linkage between specific components of the microbiome and the clinical phenotype of interest.

There is broad acceptance that functional disorders involving the brain-gut axis, such as irritable bowel syndrome, are more prevalent in females.²⁵ It remains unclear whether ACEs are a prerequisite and/or augment the clinical symptoms (visceral hypersensitivity and altered bowel habits) associated with IBS later in life and the role of epigenomics in this process.²⁶

Mechanistically, early-life stress in mice alters histone dynamics in the ventral tegmental area, a brain region critically implicated in motivation, reward learning, stress response, mood, and drug disorders.²⁷ Most of these modifications are associated with an open chromatin state that would predict active, primed, or poised gene expression, including enriched histone-3 lysine-4 methylation and the H3K4 mono-methylase Setd7. Mimicking ACE through over-expression of Setd7 and enrichment of H3K4me1 in ventral tegmental area recapitulates ACE-induced behavioral and transcriptional hypersensitivity to future stress.

Recent articles utilizing methodological advances are paving the way for improving our understanding of how chromatin modifications are linked to specific regulatory patterns of gene expression, thereby helping elucidate their causal role and context-dependent impact on gene transcription. For example, Policarpi *et al.* developed a modular epigenome editing platform that programs nine key chromatin modifications to precise loci in living cells. They employed single-cell readouts to systematically quantitate the magnitude and heterogeneity of transcriptional responses elicited by each specific chromatin modification. Specifically, they demonstrated that installing histone H3 lysine 4 trimethylation (H3K4me3) at promoters can causally instruct transcription by remodeling the chromatin landscape hierarchically. Furthermore, co-targeting H3K27 trimethylation (H3K27me3) and H2AK119 mono-ubiquitination maximizes silencing penetrance across single cells.²⁸

Neuromodulation and the brain-gut axis

Neuromodulation involves targeted stimulation or inhibition of neural activity to alter physiological processes. Acting via the brain-gut axis, such interventions can ameliorate a variety of conditions, including motility disorders, inflammatory bowel disease, and affective disorders with GI manifestations. The relationship between neuromodulation and epigenomic signatures holds promise for a new paradigm in therapeutic applications. Neuromodulation techniques, such as vagus nerve stimulation (VNS) or deep brain stimulation, manipulate specific nodes within this axis, potentially offering therapeutic benefits across various physiological and psychological conditions.^{29–32} The intersection of neuromodulation and epigenomics in the brain-gut axis is crucial to understanding the broader impact of stimulating neural pathways. For example, VNS can lead to epigenomic changes in the central nervous system that modify pain perception, inflammation, and anxiety. These changes may be mediated by alterations in methylation patterns and histone

configurations, which subsequently affect gene expression involved in neurotransmission and synaptic plasticity.³³

Innovative therapeutic strategies are being explored that exploit the relationship between epigenomic processes and neuromodulation:

1. VNS: VNS can potentially modify epigenomic marks related to the expression of anti-inflammatory pathways, which could be beneficial in treating conditions like IBD or functional GI disorders.^{29–33}
2. Sacral nerve stimulation: Sacral nerve stimulation is used for bowel dysfunction and might influence epigenomic marks associated with neurogenic inflammation and visceral sensitivity, affecting both bowel motility and pain sensation.³⁴
3. Transcranial magnetic stimulation: Transcranial magnetic stimulation can induce changes in neuronal activity that might lead to epigenomic modifications, thus influencing mood and cognitive functions in disorders that present with GI symptoms, such as depression.³⁵
4. Acupuncture: In its various configurations, acupuncture shows potential promise in reversing epigenomic changes caused by chronic pain in a neuropathic pain mouse model.³⁶ Acupuncture treatment was found to be effective in treating patients with burnout syndrome, and the epigenomic targets identified were involved in some significant disturbances of this syndrome.³⁷
5. Diet and neuromodulation synergy: Diet also plays a role in epigenomic modifications and may synergize with neuromodulation therapies, potentially shaping neural pathways and behavioral responses to modulate the brain-gut axis in obesity and eating disorders.³⁸

Epigenomics and brain-gut axis: methodological challenges

This field of research presents significant methodological challenges that must be confronted to harness its true potential. Accurate interpretation of epigenomic data and its relationship to the brain-gut axis requires careful consideration of epigenomic mechanisms' complex and multifaceted nature. Addressing these challenges is essential for advancing our knowledge and translating findings from bench to bedside. These challenges include:

1. Complexity of epigenomic mechanisms: Epigenomic regulation involves multiple control layers, including DNA methylation, histone modification, antisense interference, and non-coding RNA regulation. Disentangling the specific contributions of these mechanisms to the brain-gut axis is a formidable challenge.³⁹ Additionally, the interplay between epigenomic marks is dynamic and context-dependent, further complicating their study.
2. Sample accessibility: Directly analyzing epigenomic changes in the human brain or intestinal tissues is challenging due to the invasiveness required for tissue collection. Researchers often must rely on peripheral biomarkers or animal models, which may not fully recapitulate the human condition.⁹

3. Cell-type specificity: Epigenomic patterns differ across cell types. Therefore, understanding brain-gut axis phenomena often demands cell-specific analyses, which can be technically challenging and resource-intensive.⁴⁰
4. Microbiome Influence: The gut microbiota significantly influences epigenomic states. However, it presents a moving target due to its variability and sensitivity to various factors such as diet, medications, and stress.⁴¹ Teasing apart the host from the microbial contributions to epigenomic profiles, particularly with the brain-gut axis, requires complex and nuanced experimental designs.
5. Temporal dynamics: Epigenomic marks can change over time and in response to environmental factors. Longitudinal studies are essential to capture these dynamics, but they are more expensive and logistically problematic than cross-sectional studies.⁴² This is particularly relevant in research on adverse childhood events, in which recall bias, sampling logistics, and the isolation of specific stress effects are challenging.
6. Interindividual variation: Substantial variability in epigenomic marks between individuals due to genetic variation and life history is well described. This variability can confound analyses and make identifying diagnostic epigenomic biomarkers complex.⁴³
7. Analytical challenges: The vast data generated in epigenomic studies necessitate sophisticated bioinformatic tools and statistical models to interpret. Errors in data analysis can lead to incorrect conclusions, making robust and replicable analysis methods paramount.⁴⁴

Epigenomics and brain-gut axis: strategies to address methodological challenges throughout the lifespan

A successful strategy to address the challenges of conducting research on the brain-gut axis throughout the lifespan will inherently be cross-disciplinary and require long-term human resource support and the application of evolving methods. We propose that a successful strategy will include the following components:

1. Cross-disciplinary collaboration with expertise in epigenomics, CNS and GI neuroscience (pediatric and adult), microbial ecology, statistics, and bioinformatics can facilitate a comprehensive understanding of brain-gut axis phenomena.
2. Research strategies and recruitment plans that address differences in epigenomic profiles based on biological sex and ethnicity.
3. Employ translational research strategies using validated animal and organogenesis models to perform mechanistically-focused studies.
4. Innovative technologies such as single-cell epigenomics and *in vitro* imaging of epigenomic changes can provide more precise information about cell type-specific epigenomic patterns and real-time DNA-chromatin dynamics.

5. Development of non-invasive or minimally invasive assays and biomarkers to monitor human epigenomic changes associated with brain-gut axis signaling.
6. Leveraging existing and emerging extensive data resources, including biobanks and longitudinal cohort studies. Prospective studies will likely require a multi-institutional model with support from a centralized review and monitoring program, a core tissue repository, and biostatistics and bioinformatics expertise.
7. Employ longitudinal study designs that capture the temporal dynamics of epigenomic marks and their relationship to clinical outcomes across the lifespan.
8. Integration of multi-omic data (genomic, epigenomic, transcriptomic, metabolomic, and microbiome) to provide a holistic view of the factors impacting the brain-gut axis.
9. Continuous refinement of bioinformatic tools and machine learning algorithms to manage the complexity and enhance the analysis of epigenomic datasets.

Conclusions

The intricate interplay between epigenomics, the brain-gut axis, and early life stress presents a profound but challenging study area with significant implications for health across the lifespan. Early life stress, encompassing a range of stressful experiences during childhood, such as abuse, neglect, or family conflict, has lasting impacts on both physical and psychological well-being. Epigenomic mechanisms provide potent insights into how such early adversities can lead to long-term changes in gene expression, potentially influencing the development and function of the brain-gut axis. The brain-gut axis is a critical communication pathway, and stress can significantly affect GI function. During critical developmental windows, the gut is susceptible to stress-related neuroendocrine and immune modifications resulting from altered epigenomic programming. Early life stress can disrupt the hypothalamic-pituitary-adrenal (HPA) axis regulation, which is crucial for stress response modulation. Epigenomic alterations, particularly in genes related to the HPA axis, such as the glucocorticoid receptor gene (*NR3C1*), have been observed in response to early life stress. These modifications may produce long-term changes in the way individuals respond to stress and can influence susceptibility to various disorders, including those associated with the brain-gut axis, such as depression and IBS. Early life stress has been linked to changes in gut motility, intestinal barrier function, and the gut microbiome, all of which can have lasting effects on GI health and contribute to the pathogenesis of GI disorders. Emerging treatments, including neuromodulation and medicinals based on epigenomic and pharmacogenomic research, hold promise for targeted interventions in the future.

Funding

JWW receives grant support from the National Institutes of Health (NIH R01DK058913; NIH R01DK122350; NIH P30DK034933; NIH UG3NS115108, NIH-HEAL Program; and NIH-SBIR 073133571).

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Examples of epigenomic modifications and epigenome modifiers that impact the epigenome and are used in treating IBD and IBS (b)

Table 1.

(a) Examples of epigenomic modifications / modifiers of gene regulation			
Molecular Entity	Mechanism	Presumed Causality	Transgenerational Inheritance
DNA methylation	Direct silencing of gene expression	Chronic stress	Yes, evidence from mice
Super-enhancers	Activation of multiple genes in a coordinated manner	Acute stress, viral infection, and immune reactions	unknown
Histone methylation	Silencing of gene expression	Normal function	unknown
Histone acetylation	Activation of gene expression	Normal function	unknown
Chromatin remodeling	Open or close chromatin for access by transcription	Acute injury and chronic stress, normal development	unknown
microRNAs	Regulation of gene expression at 3' UTRs	Normal function	Yes
Piwi RNAs	Involved in mRNA splicing	Normal function	Yes
Long noncoding RNAs	Act in catalysis without protein involvement	Normal function	Yes

(b) Specific drugs that are used for the treatment of inflammatory bowel disorders		
Medication	Mechanisms	Conditions
Azathioprine and 6-Mercaptopurine	These immunosuppressive agents are used primarily in inflammatory bowel disease (IBD). They inhibit purine synthesis, affecting DNA and RNA synthesis, and have been shown to influence epigenetic mechanisms, including DNA methylation	Crohn's Disease, Ulcerative Colitis
Methotrexate	This folate antagonist interferes with DNA synthesis, repair, and cellular replication. It has been noted to impact epigenetic regulation through alterations in DNA methylation	Used off-label for IBD, particularly Crohn's Disease.
Sulfasalazine	This anti-inflammatory medication used in IBD has been shown to influence histone deacetylase (HDAC) activity, impacting chromatin structure and gene expression	Ulcerative Colitis
Biologics-(Infliximab, Adalimumab)	These anti-TNF agents reduce inflammation by targeting specific cytokines. Emerging evidence suggests they may also exert epigenetic effects by modifying cytokine gene expression through DNA methylation and histone modification	Crohn's Disease, Ulcerative Colitis
Corticosteroids	Commonly used in both IBD and severe IBS, corticosteroids influence gene expression by altering chromatin structure via the glucocorticoid receptor, which can bind to DNA and modulate transcription	Crohn's Disease, Ulcerative Colitis, Severe IBD
Antidepressants (SSRIs and TCAs)	These medications can modulate neurotransmitter levels, and recent studies suggest they may have epigenetic effects by altering histone acetylation and DNA methylation	Used in irritable bowel syndrome (IBS) primarily for their analgesic properties

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Rifaximin

This antibiotic, used for IBS-D (diarrhea-predominant IBS), can alter the gut microbiota, which indirectly influences the host epigenome through microbial metabolite-mediated mechanisms

IBS-D

HDAC, histone deacetylase; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; IBS-D, diarrhea-predominant irritable bowel syndrome; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants; TNF, tumor necrosis factor; UTRs, untranslated regions.