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Can Understanding Gut-Brain Axis Biopsychosocial Pathways Improve Clinical Reasoning?

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A B S T R A C T

Most nurse practitioners (NPs) practice in primary care settings. Cognitive tools to inform and advance NP understanding of biopsychosocial mechanisms can support early recognition, interdisciplinary collaboration, interventions, and prevention of negative outcomes. We describe the development of a model to support NP consideration of gut-brain axis evidence-based pathways, contributing variables, and related health outcomes. The model's outcomes are factors associated with homeostasis or disruption of biological, psychological, and social systems. This cognitive tool aims to support NP awareness of multidomain gut-brain axis relationships to consider with differential diagnoses and clinical treatment of the "whole body system."

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Introduction

Most nurse practitioners (NPs; 88.9%) are certified in primary care, and full-time NPs (59.4%) see 3 or more patients each hour and write an average of 21 prescriptions daily.[1] Patients seek primary care for many various reasons. Top reasons for primary care visits include symptomatic conditions of abdominal symptoms, headache, and fatigue.[2] Each health assessment must be honed to the unique subjective and objective findings. Given these considerable demands, and the complexity and often ambiguous nature of complaints, having cognitive tools that bridge multiple domains of wellness can support clinical reasoning, health assessment, and treatment of patients.

An area that is providing rich evidence around biopsychosocial symptom relationships with health outcomes is the gut-brain axis (GBA). Clinicians have long witnessed and sought to better understand the manifested links between gastrointestinal functioning and the central nervous system. Considering what is known and applying it clinically can support identifying root causes and inform treatment options. This is relevant to advanced nursing practice because it is a holistic approach and because there are multiple modifiable constituents in the domains of the model that are important for translation and application in the clinical setting.

Multiple models exist on how the GBA influences health and well-being. When considered separately, these models generate predictions about relationships between the included variables. Here, we examine the collective frame of reference that is created when GBA models are integrated and describe the development of the GBA Pathways Model to synthesize understanding and offer a cognitive tool for NPs in primary care settings.

The GBA Pathways Model is a combination of 7 intersecting conceptual models. First, we describe the basic concepts of each of the included models and then discuss how the attributes of these models, when integrated, allow for a new perspective for supporting NP knowledge and clinical reasoning, thus improving understanding of the relationships among biological, psychological, and social variables that have the capacity to influence health through the GBA. The model is not intended to be exhaustive, nor are all domains intended to be completely independent of other domains. The model's focus on potential subjective and objective health assessment findings is complimentary in nature to the excellent work that has been done around the GBA and diseases such as autism, Alzheimer disease, Parkinson disease, stroke, irritable bowel syndrome, vascular dementia, depression, anxiety, and many others.[3-7] The GBA Pathways Model can be applied to populations across the lifespan. The report concludes with a focused example of how and why having a model like this is relevant and valuable in studying and clinically supporting adolescent health.

In the last decade, interest in the GBA and its potential relationship with health and well-being has flourished. There was an indication for the benefits that could emerge with a model delineating the comprehensive GBA pathways and support of research, collaboration, and clinical practice in this burgeoning field. Integrating applicable models develops a collective state of the science for clinicians' health assessment exploration of GBA pathways that relate to human biopsychosocial well-being.

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Methods

Model integration in this report focused on bidirectional pathways; bottom-up pathways, the pathways through which the microbiota and digestive physiology affect brain and behavior through the GBA, and top-down pathways in which brain and behavior affect biological processes. Further, contextual factors such as environment and diet are integrated. The integration included 7 theory models: (1) Polyvagal Theory,[8] (2) Hologenome Theory,[9] (3) Holometabolome Theory,[10] (4) Biopsychosocial Model,[11] (5) Gut Microbiome and the Gut/Brain Axis in the Modulation of the Stress Response Theory,[12] (6) Agustí Model, depicting the relationships between cognitive functioning, mood, obesity, and the microbiome through the GBA,[13] and (7) the Mirobiota-Gut-Brain Axis-Heart Shunt Model.[4,5] The postpositivist totem of incorporating creative and diverse methods for interpreting and enhancing nursing research and designing effective care strategies for addressing the needs of diverse people relates well to the physical and psychological/behavioral mechanisms included in the GBA Pathways Model.[14]

Polyvagal Theory

Polyvagal Theory, developed by Stephen Porges[8] in 1995, is characterized by a hierarchical system of strategies to interpret and regulate the body's response to feeling safe or unsafe. It is a neurophysiologic model linking autonomic nervous system (ANS) regulation to physiologic, psychological, and behavioral processes.[8] The theory is best captured by a postpositivist philosophical approach in which describing, explaining, and predicting phenomena accepts both quantitative and qualitative data;[14] for example, on the relationship between the qualitative and individual perception of safety vs the quantitative neurobiological response. Porges[15] suggests that the ANS, primarily through the vagus nerve, behaves in ways we previously have not understood. This theory outlines a bidirectional neurobiological communication system by the ANS that prefers social engagement and places this strategy for preserving a safe state at the pinnacle of the evolutionary response to stress. Of clinical significance, the theory states that the physiologic state of a person sets limits on the possible ranges of both behavior and psychological experiences.[15]

The hierarchy of strategies suggested by Polyvagal Theory is what Porges[15] refers to as the social engagement system (SES), where social engagement is the highest form of functioning. The SES keeps the "vagal brakes" stopping sympathetic response as long as the engagement with our environment allows us to perceive ourselves and our environment as safe. If social engagement is unsuccessful at maintaining a perception of safety, the SES releases the vagal brake to allow first, the sympathetic (fight or flight), and then, the unmyelinated (freeze, feign death, shut down) responses to be activated.[15]

For people who constantly perceive their environment as unsafe or for those whose neurodevelopment produced errors in the SES, such as individuals with autism spectrum disorder, an array of psychophysiological problems may be noted. Polyvagal Theory suggests that the basis for these difficulties lies within neurophysiologic and biological imbalances. Clinically objective findings, such as difficulties making eye contact, averted gaze, and issues with the extraction of human voices from background noises, as well as ingestion/digestion difficulties, are all purported responses to chronic stimulation of the older vagal pathways.

Chronic stimulation negatively influences the hypothalamus-pituitary axis (HPA).[15] This HPA axis stimulation results in the production of glucocorticoids by the adrenal cortex. Multiple examples of the relationship between the model and potential applications for clinical practice exist, including developing methods for improving communication and situational awareness; monitoring the sense of perceived safety in a person's environment (home, community, school, etc); and monitoring, educating, and supporting interventions around the impact of the presence of elevated levels of glucocorticoids and its correlations with a host of symptoms that produce pathologies such as irritable bowel syndrome (IBS), Alzheimer disease, and autism[16]; cardiovascular disease, rheumatoid arthritis, psychiatric disorders (depression, psychosis, dementia, bipolar disorder), inflammation, and metabolic syndrome,[17] all of which have clinical implications.

Polyvagal Theory's foundation rests on the importance of environmental influences in producing or influencing the perception of safety. Furthermore, this theory provides a clinical tool for understanding potential implications for self-regulation, psychological therapies, and adaptive functioning as well as indications for research regarding neurobiological triggers, inborn errors, and physiologic imbalances. It supports the development of clinical treatments that focus on the relationship between physiologic states, the psychological impact of those states, and the ranges of behavior they have the potential to inhibit or produce. The additional models' domains increase the breadth of concepts, supporting a more comprehensive understanding involving multidomain biopsychosocial mechanisms and development of holistic clinical interventions. Each subsequent theory model and the process that supported their addition to the final model as well as their clinical significance are described.

Expanding the GBA Pathways Model With the Microbiome Domain

Until the mid-1880s, the microbiome remained undiscovered. A pediatrician named Theodor Escherichia first discovered bacteria that lived in the gut of healthy and ill children.[18] This work led other scientists to start exploring the bacteria in and on the human body, and in the first decade of the 21st century, the term "human microbiome" was born.[18] Thoughts and theories about the relationship between humans and their microbiome began to emerge, including Holometabolome Theory.

Holometabolome Theory

In 2011, just a decade ago, Holometabolome Theory[10] was developed to describe domains and relationships of metabolites produced by microbes and the human host on each entity's overall metabolism. Holometabolome Theory has the strength of including domains that are clear and have a capacity for clinical measurement, such as stress, antibiotics, diet, age, host metabolism, brain development, and function. The outcome of this theory, human brain development and function, are of particular interest and are an important strength. Holometabolome Theory does not define health and behavior outcomes, thus integrating this model allows for the inclusion of outcome variables that strength the model and the clinical applicability.

Hologenome Theory

Hologenome Theory[9] is very similar to Holometabolome Theory. It expands the term "human microbiome" and describes the concepts that summarily create the "holobiont." The holobiont is a supra-organism that is the sum of the human host genetic material and all its associated microbes genetic material.[9] The diagram of the theory depicts how this coexistence has bidirectional relationships between domains that allow both entities to have an effect on each other.[10]

The relationship between microbes and the human host was initially regarded as commensalism (neither entity having any effect on the other), but emerging evidence has defined the gut

microbiota as having both mutualistic (synonymous with symbiotic) and/or parasitic interactions (beneficial to the microbes but detrimental to the human host).[4,5,10] The theory's strengths are that it has clear and well-defined, measurable relationships. The bidirectionality of the relationships makes causal relationships harder to test; however, exploration of moderators in this theory could potentially be tested. This theory hypothesizes a moderator of the human genome on the microbial genome through immunity and nutrition and the microbial genome on the human genome through toxins and beneficial metabolites.[10]

The outcome of this model is health. Health is illustrated as a continuum from health through transition into disease. The outcome, as a continuum, is vague, and the integration of multiple models allows the benefit of adding subdomains that are quantitatively measurable and translatable to practice. The clinical applications of this theory are immense, and the number of studies directed to understanding the impact of these relationships has grown significantly. The microbiome is shaped by many modifiable attributes that have the potential to be intervened on, including diet, medications, hormones, tools to deal with stress, and prebiotics and probiotics.

The Process of Integrating the Theories

"Environmental factors" was a shared concept between Holometabolome and Hologenome Theory, making a link to support their integration. Both theoretical models illustrate the effect of environmental factors on the microbiota and the human host. Furthermore, they both describe a bidirectional relationship between the microbial and human genome. Holometabolome Theory provides this through the lens of metabolites, and Hologenome Theory provides this through the lens of genetics.

The outcome constructs of integrating these theories are the relationships between genetics and metabolic effects. However, the Holometabolome Theory outcome focuses on brain development and function, whereas the Hologenome Theory outcome focuses on a spectrum of human health across a continuum from health to disease as its outcome. Overlaying these 2 theories and then integrating the combined model with Polyvagal Theory strengthened the connections for studying the human environmental response and how psychological, biological, and social factors symptomatically reveal themselves across multiple domains. The holistic evaluation of the combined symptomatic expression of these 3 interrelating domains is at the heart of nursing practice as we seek to assess, plan, and intervene with the "whole" person.

Biopsychosocial Theory

Biopsychosocial Theory[11] is essential in that it depicts the interconnectedness of the 3 conceptual domains (biological, psychological, and social domains) and illustrates the resulting impact of these relationships. Engel, in his *Critique of Biomedicine*, outlined concerns about biomedical thinking at that time. He stated that the appearance of illness occurs at the intersection of diverse causal factors, including molecular, individual and social levels.

Drossman[19] used Engel's theory to look at gastrointestinal illness. Drossman's representation of the biopsychosocial theory conceptualizes pathogenesis through the interplay of these 3 domains through the enteric nervous system (ENS) and central nervous system (CNS).[11,19] It further depicts resultant symptoms, health outcomes, and behaviors.[19] The interplay between the ENS and CNS is bidirectional cross talk that has a top-down effect on the intestines through the brain's experience of stress and/or traumatic events on the emotional system or bottom-up through the gut's experience of infection, inflammation, food, and an imbalanced microbial composition.[20] Psychosocial factors (life stress, coping, social support, and a person's psychological state) and physiologic factors (bowel sensation, motility, inflammation, and altered bacterial flora) comprise the realms of factors influencing the emergence of symptoms and behaviors. The symptoms and behaviors have adverse outcomes, negatively affecting quality of life.[21] This model speaks more specifically to the biopsychosocial factors interacting through the GBA as well as providing greater clarity to domains and the relationships among them.

Gut Microbiota and GBA in the Modulation of the Stress Response Theory

The Gut Mircobiota and GBA in the Modulation of the Stress Response Theory describes how emotional and physical stressors may cause multilevel disturbances through the GBA via the CNS and ANS as well as the ENS connection of the sympathetic and parasympathetic arms of the ANS.[12] Thakur et al[12] report that evidence exists that disturbances are occurring that affect visceral perception and subsequently, the perception and emotional response to visceral events.

The theory depicts the relationships between the constructs of emotional stressors, physical stressors, and the effect through the GBA. The illustration's initial domain is stress, which is shown to affect the brain and in turn is bidirectionally interacting with the GBA through neuronal, endocrine, and immune messaging.

The model describes the result of stress on gut microbiota as dysbiosis, which is the imbalance of normally present healthy gut microbes. Dysbiosis produces functional gastrointestinal disorders and inflammatory bowel disorders in the gut,[12] which in turn affect the brain through the GBA that has functional mechanisms in the neuroendocrine and neuroimmune systems as well as the ANS. The effect on the brain is the potential manifestation of visceral pain, anxiety, cognitive deficits, abnormal behavior, autism, and other psychological disorders.[12]

A strength of this theory is that there are a limited number of constructs, and the constructs are more fully defined. The factors of this model that are most easily testable and quantifiable include biomarkers, such as γ-aminobutyric acid, short-chain fatty acids (SCFAs), inflammatory cytokines, and 5-hydroxytryptamine precursors, which are depicted as the result of dysbiosis. Although dysbiosis is shown to have adverse health-related outcomes for the gut and brain, future research will need to elucidate the causal factors and mechanisms by which these relationships work. Of interest to exploratory research, this theory contains primarily bidirectional relationships, which creates complexity for testing these relationships and determining causality. Finally, this theory is useful to study the ill effects of multidimensional stress on the body. Future evolutions of this model could explore concepts that produce protective effects, support homeostasis, and even resilience.

Interplay Between the Gut-Brain Axis, Obesity, and Cognitive Function

The Interplay Between the Gut-Brain Axis, Obesity, and Cognitive Function Theory[13] was published in 2018. Domains of the vagal pathways of the GBA are included, as previously discussed in polyvagal theory, and cognitive functioning, mood, obesity, and dysbiosis, as previously discussed in the Holometabolome and Hologenome theories. This newest theory describes more precisely the directional relationships between the domains. It proposes that obesity-associated microbiota with the nutritional intake of sucrose and high-fructose diets results in dysbiosis. This dysbiotic drift in the numbers and types of gut microbiota present is proposed to cause negative mood outcomes, including increased anxiety and

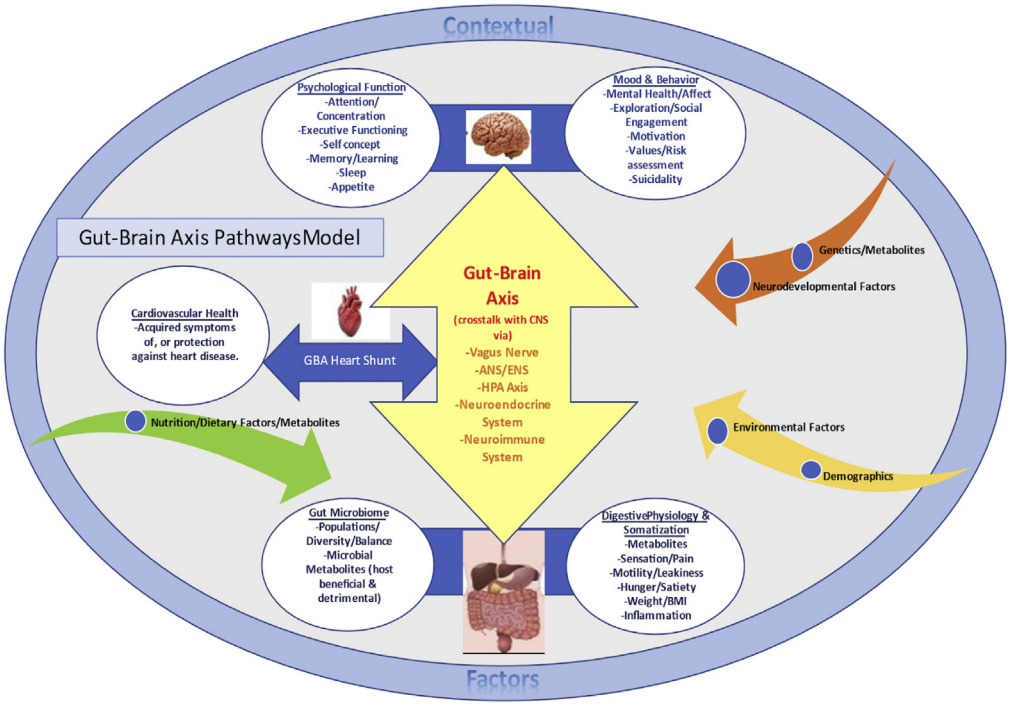

Figure. Gut-brain axis (GBA) pathways model. ANS = autonomic nervous system; CNS = central nervous system; ENS = enteric nervous system HPA = hypothalamus-pituitary axis.

depressive moods, increased social alterations, and sensitivity stress. The theory further proposes a causal link between this obesity-related dysbiosis and decreased attention, executive function, and decreased cognitive function with hippocampal dysfunction, impaired memory, and altered explicit memory.[13] Agustí et al[13] report the downstream effects of HPA dysregulation with overproduction of glucocorticoids, altered levels of neurotransmitters and SCFAs, and activation of an inflammatory milieu that causes an increase in neuroinflammation. This model adds significantly to the contextual domains and theoretical underpinning of the potential effect of the GBA as a mechanism for health outcomes.

Microbiota-Gut-Brain-Neuro-Endocrine Axis Co-Metabolism Model

The Microbiota-Gut-Brain-Neuro-Endocrine Axis Co-Metabolism Model provides an overview of either the positive or negative interplay of these systems on a proposed Microbiota-Gut-Brain Axis-Heart Shunt.[4,5] The authors describe how lifestyle characteristics of environment, diet, and nutrition bidirectionally impact health in positive or deleterious ways. When the human system experiences stress, the consequences of interactions allow gut-derived and liver-derived transformations of microbial toxins that contribute to heart disease, dysbiosis, and mental disease.[4,5] When the same system experiences an optimal environment, beneficial SCFAs, hormones, and neurotransmitters produce a positive impact on well-being and support prevention of both heart and brain diseases.[4,5]

Description of the Newly Developed GBA Pathways Systems Theory

The GBA Pathways Model (Figure) is designed to bring together these overarching multidisciplinary domains and relationships supported by the integration of these 7 models. The resulting model contains 10 overarching concepts and includes multidomain outcome constructs from cognition, mood, behavior, various physiologic outcomes of digestive, immune, cardiovascular, and neurologic functioning.

The GBA Pathways Model (Figure) is designed to diagrammatically reflect the domains and relationships supported by the complete model. The model is simplified into 10 constructs, 3 of which are contextual domains, including environmental/demographic factors, genetic/metabolites and neurodevelopmental factors, and nutrition/dietary factors. The other relational domains include the GBA, the GBA heart shunt, the gut microbiome and their associated products, digestive physiology and somatization, mood, and behaviors, and psychological function.

The GBA Pathways Model focused heavily on how a wide variety of multivariate sign and symptom domains interact and coalesce to produce health outcomes. The domains and concepts of the model remain true to the theory of origin but are integrated where they overlap to increase the scope and or depth of collective models through integration. The diagrammed GBA Pathways Model begins with the GBA and its components (at the center of the model). From the GBA, the heart shunt impacts cardiovascular health either positively from SCFAs, neurotransmitters, and hormones, or negatively from microbial-produced toxins (lipopolysaccharides, trimethylamine-*N*-oxide, and others) or toxins produced by the transformation of liver-derived toxins from liver-microbiota co-metabolism.[4,5] The GBA at the center is a bidirectional arrow that points upward to the 2 domains of brain-related psychological functioning and mood and behavior and downward to the 2 domains of the gut microbiome, and digestive physiology and somatization.

Within the psychological domain, there are 6 subdomains, comprising attention/concentration, executive functioning, self-concept, sleep, impulsivity, worry, and appetite.

Within the mood and behavior domain, there are 7 subdomains, including stress, anxiety, behavior (autistic), lack of pleasure and depressed mood, self-injury, and suicidality.

Within the digestive physiology and somatization domain, there are 6 subdomains, comprising sensation/pain, motility/leakiness, hunger/satiety, weight/body mass index, somatization, and inflammation.

Within the domain of the gut microbiome are the 3 subdomains of altered diversity, balance, metabolites.

It is important to note that the model is not intended to be exhaustive. In future development, each of the concepts in the model could be expanded more macroscopically to include associated diseases, psychopathologies, or microscopically toward cellular level functioning and metabolites, hormones, neurotransmitters, cytokines, chemokines, and many more.

Population Exemplar: Adolescents

As a population health exemplar, current health trends of adolescents are showing a greater prevalence of obesity, mental disorders (anxiety, depression, and behavioral), attention difficulties, sleep disturbances, and suicide. The consequential significance of understanding mechanisms for these health outcomes through the GBA and effectively intervening is urgent.[22] The GBA allows for complex communication between paths as described in this report and illustrated in the GBA Pathways Model: the endocrine system via the HPA and the immune system via the cytokines and chemokines.[23] As an example, the ENS houses an estimated 95% of the body's serotonin and 70% of the body's cellular immunity,[24] thereby providing a GBA pathway for significant relationships between mood and inflammation.

Of the Centers for Disease Control and Prevention's adolescent priority health concerns previously mentioned,[22] there are studies that are looking at multiple areas of GBA-related health outcomes, including sleep,[25] cognition and attention,[24] dietary behaviors and weight,[13] mood and behavior,[13,25-28] and injury and violence, including suicide.[29] The GBA Pathways Model provides a method for evaluating the interrelated impact from multiple domains. A further example includes the relationship between sleep, anxiety, and appetite, which have a GBA Pathways Model basis for exploring these relationships within GBA-related mechanisms.

Effectively exploring relationships between such biological signs and psychological and social symptoms presenting in combination during adolescence could provide the ability to predict meaningful transitions along the continuum of healthy to unhealthy outcomes and intervene on the recipe of symptoms that produce more severe negative outcomes and diagnoses. To do this effectively, including this level of thinking and assessing at the clinical level is essential.

We are endeavoring, with this model, to support improving the understanding of the biopsychosocial landscape of adolescence, biobehavioral circuits, and antecedents to these multisystem relationships and the impact on outcomes. Further, built intentionally into its contextual factors, is the foundational appreciation for the dynamic, unique, and varied attributes of each person's journey with regard to their genetics, neurodevelopment, nutrition, and environment.

Conclusion

Providing community-based primary care requires multidisciplinary collaboration across micro, meso, and macro levels. As we include these attributes into our clinical examination practices and our differential diagnoses, we improve the recognition of and impacts from the "whole" system. This in turn supports research where clinical findings can be retrospectively studied for emerging patterns and give way to tests such as for the microbiome or metabolome. These tests may become a clinical laboratory assessment as our appreciation of the impacts of GBA-related mechanisms deepens. Further, it leads the way for the development of new clinical interventions and therapies that affect biological, psychological, and social realms of well-being.

The goal of this project was the development of an integrated model to support clinical thinking and research exploration of symptom relationships that affect biological, psychological, and social health and have mechanistic pathways through the GBA. The collective perspective of the model as a cognitive tool produces a robust context for informing health assessment, expanding differential diagnoses, and providing insight about potential treatment plans. It can also support doctor of nursing practice and PhD nursing research studies and collaborations across an array of other multidisciplinary scientific pursuits for further elucidating information around the GBA pathways.

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