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Interoception, Trait Anxiety, and the Gut Microbiome: A Cognitive and Physiological Model

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Trait anxiety is characterized as a constant and often subliminal state that persists during daily life. Interoception is the perception of internal states and sensations, including from the autonomic nervous system. This review aims to develop a predictive model to explain the emergence, manifestations, and maintenance of trait anxiety. The model begins with the assumption that anxiety states arise from active interoceptive inference. The subsequent activation of autonomic responses results from aversive sensory encounters. A cognitive model is proposed for trait anxiety that includes the aversive sensory components from interoception, exteroception, and proprioception. A further component of the hypothesis is that repeated exposure to subliminal anxiety-evoking sensory elements can lead to an overgeneralization of this response to other inputs that are generally non-aversive. Increased uncertainty may result when predicting the sensory environment, resulting in arbitrary interoceptive anxiety responses that may be due to unjustifiable causes. Arbitrary successful or unsuccessful matching of predictions and responses reduces the individual's confidence to maintain the anxiety trait. In this review, the application of the proposed model is illustrated using gut microbial dysbiosis or imbalance of the gut microbiome.

Keywords: Anxiety • Brain • Cognition • Gastrointestinal Microbiome • Models, Psychological • Stress, Physiological

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Background

With a prevalence of 7.3% worldwide, anxiety disorders are among the most common psychiatric disorders reported [1]. Anxiety is a multisystem response to danger or a threat that may be real or imagined and is often excessive [1,2]. Anxiety involves memory and past experiences [1,2]. Anxiety manifests through biochemical changes and activation of the sympathetic nervous system, putting the body in a state of heightened attention and vigilance, also known as the fight-flight response [1,2]. This evolutionary response increases the chances of successfully overcoming perceived threats [3]. Feelings associated with anxiety include stress, nervousness, and unease, resulting in unpredictable outcomes [4].

Trait anxiety is characterized as a constant and often subliminal state that persists during daily life [5]. Interoception is the perception of internal states and sensations, including the autonomic nervous system [6]. While this previously vital evolutionary adaptive response remains deeply embedded, anxiety increasingly represents a modern evolutionary burden that results in human suffering and disease [3,5]. However, unlike anxiety states, which are transient reactions to specific and often distinct situations, trait anxiety is a consistent and generalized predisposition to react to a variety of situations consistently [5,7].

Predictive models may be used to explain the emergence, manifestations, and maintenance of trait anxiety [8]. It is possible to develop a model that begins with the assumption that anxiety states arise from active interoceptive inference [8,9]. The subsequent activation of autonomic responses results from aversive sensory encounters, and repeated exposure to subliminal anxiety-evoking sensory elements can lead to an overgeneralization of this response to other inputs that are generally non-aversive [8]. Predictive coding of interoceptive inference may also explain how trait anxiety may arise from frequent anxiety states due to environmental and biological factors [8]. Overgeneralizing sensory experiences and uncertainty in prediction error minimization in a bi-directional manner will be used to illustrate how gastrointestinal aversion, altered gut microbiome, and brain interactions may lead to an interoceptive response [8,10,11].

This review aims to develop a predictive model to explain the emergence, manifestations, and maintenance of trait anxiety. The model begins with the assumption that anxiety states arise from active interoceptive inference. The subsequent activation of autonomic responses results from aversive sensory encounters. Arbitrary successful or unsuccessful matching of predictions and responses reduces the individual's confidence to maintain the anxiety trait. In this review, the application of the proposed model is illustrated using gut microbial dysbiosis or imbalance of the gut microbiome.

A Predictive Coding Framework for Sensory Processing in Trait Anxiety

Predictive coding is based on recognizing that the brain's main function is to analyse varied and often incomplete sensory information to enable the individual to function [12,13]. Given this ambiguity, several possible hypotheses fit the requirement for sensory information processing. The brain selects from these hypotheses in a Bayesian manner, which involves a previous experience of probability in any situation [12,13]. When a hypothesis is selected, this generates predictions about likely future sensory input [12,13]. However, when these predictions are inaccurate, prediction errors are generated, leading to either revision or abandonment of the hypothesis in question [12,13].

Previous studies have shown that these perceptual hypotheses are reciprocally constructed from various sensory modalities that commence as independent systems [9,14]. Then, unimodally registered sensory information is sent through the cortical hierarchy from low-level processing regions to high-level processing regions, where multimodal concepts and predictions originate [9,14]. Studies have demonstrated the relationship between exteroceptive, body-external, signal processing, perceptual, and behavioral abnormalities [9,14,15]. For example, in 2014, Wilkinson demonstrated how the symptoms of schizophrenia, such as hallucinations, may be explained through a disturbance in the error minimization process leading not only to a shift in perceptual attention and ambiguity of the unfiltered data stream but also to faulty associations between incoming sensory data and internal representations of the sensory cause [15]. Recent studies on the relationship between interoceptive signal processing and perceptual and behavioral abnormalities have shown that emotional states, including anxiety states, derive from active interoceptive inference [9]. The generation of physiological responses to change the incoming sensory information may occur to match prior expectations [16,17]. Therefore, when prediction errors are minimized through active inference, the matching concept's affective content is released, resulting in the emotional experience associated with a specific situation [9,18]. Specifically, the enacted changes of the visceromotor system that adjust autonomic reflexes, such as heart rate, respiratory rate, and smooth muscle fibers, resulting in the emotional experience and behaviors of anxiety states [6,19,20].

For successful systemic integration of the above information in higher-order mental processes, such as emotion regulation and decision making, effective inter-network communication in higher cortical regions is inevitable [14]. Therefore, there is a fine-tuned interplay between different functional networks, such as attention networks, default mode networks, and other control networks, to monitor environmental

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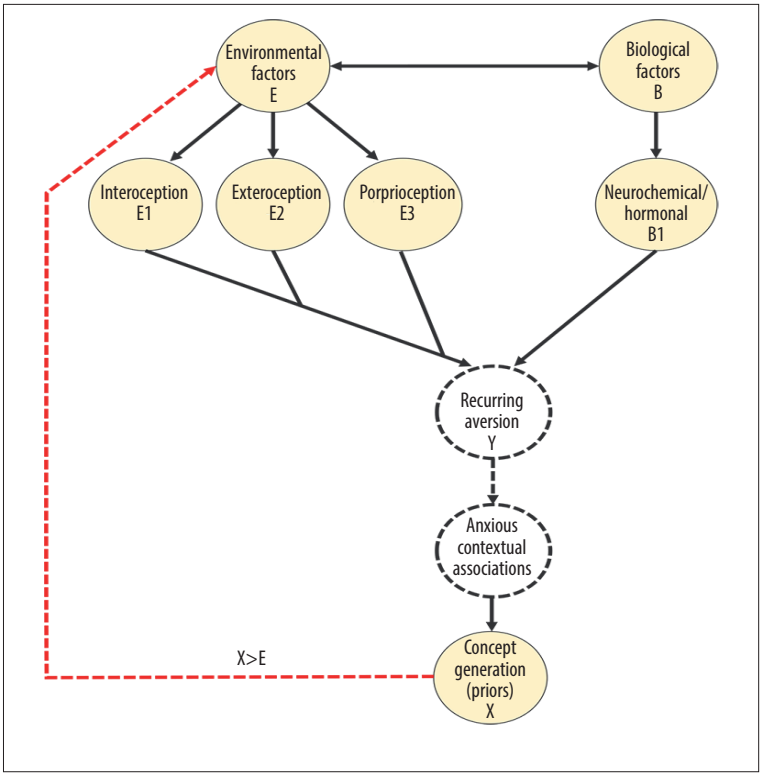

Figure 1. Interoception, trait anxiety, and the gut microbiome: A cognitive and physiological model. The model shows the emergence of contextual anxiety associations through overgeneralization. In this hypothesis, even if one of the lower sensory modalities (E1, E2, or E3) have an adverse or recurrent component (Y), this eventually affects the concept (prior X), which can lead to a negative association of the whole concept and its individual elements [8,11]. This process is driven by bi-directional prediction error minimization, where prediction errors convey information of the sensory environment (E), and the prior (X) the experiential data of predicted cause and neural response [9,12].

changes [9,19,21,22]. The weighting of signal significance and the switching between states supervene the facilitation of every hypothesized action [9,19,21,22].

The Emergence and Manifestation of Trait Anxiety as an Aversion in the Gut

In 2017, Raymond et al proposed that the overgeneralization of incoming sensations in the brain associated with a biological predisposition or exposure to a negative environment or experience could result in aversive learning that manifests in frequent anxiety states [8]. The emergence and manifestation of trait anxiety as an aversion response to the gut microbiome is the basis for the model proposed in this review. Raymond et al proposed that heightened threat awareness and avoidance mutually reinforced each other in trait anxiety, with aversive behavior and avoidance reward behavior [8].

Figure 1 illustrates the effect that environmental and biological states can have on generating prior expectations on deep cortical layers and hierarchically high cortical regions by generating stable associations early in life. When the brain attempts to allocate sensory causes in a spatiotemporal manner, it is unimodally received from proprioception, exteroception, and interoception encoded and forwarded up the cortical hierarchy the individual components become multimodally coupled [9,16,19]. Therefore, when an external event is registered for the first time, the brain attempts to weigh the salient and unknown sensory evidence against learned causes on each cortical level [9,16,19]. Precision-weighting then occurs in an ascending process [9,16,19]. Prediction errors are weighted and minimized by inhibitory error and state units and projected by pyramidal error units to update pyramidal state units on the next higher cortical level [17,23-25]. Since a newly encountered stimulus depicts high saliency and possibly no congruent conceptualized response, synaptic depression in the form of active inference can only be implemented in a limited way to resolve the error [25-28]. The salient sensory stimuli are encoded and inferred to concepts, which neural codes best match, resulting in a dual reaction [21]. If components of the novel detected stimuli are aversive, the active interoceptive inference is generated as a general autonomic response to conceptually similar stimuli [21]. This partial error minimization then gives rise to the typical symptoms of anxiety [20]. The remaining prediction errors are then forwarded to enrich similar concepts with new sensory detail across all cortical hierarchies in an integrative manner [20]. Should the individual find themselves in a similar situation, a more accurate prediction of the sensory cause and a response can be generated, leading to a context-specific anxiety association and emotional response [8,13,29].

It is possible to hypothesize that if the cause of the aversion is not obvious, recurrent exposure may lead to an integration of the anxiety component across various contexts to strengthen a generalized anxiety response to unjustifiable sensory

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causes [8,13,29]. **Figure 1** shows the proposed model of the emergence and manifestations of trait anxiety [8]. Even if one of the lower sensory modalities (E1, E2, or E3) have an adverse or recurrent component (Y), this eventually affects the concept (prior X), which can lead to a negative association of the whole concept and its individual elements [8].

Therefore, when a negatively associated concept is being formed, any specific neuronal code matching sensory information, whether negative or positive, could evoke the coupled, conceptualized, and interoceptive response [8]. Active inference may manifest in anxiety toward possibly unexplainable causes [8]. Furthermore, it is possible that if attention is consistently weighted toward previous experiences rather than actual sensory evidence (X>E), this reinforces aversive behaviors by reducing prediction errors through a rewarding action, such as avoidance behavior [6,8]. The reward then results in repeated behaviors, constant confirmation of the threat, leading to trait anxiety due to the association of aversive content in an increasing variety to environmental stimuli [8].

Aversive content can originate from various sources. Besides specific negative sensory experiences, biological factors, such as genetically predisposed maladjustment of neurobiological and endocrine systems may be involved (B1) [8,29]. By causing high sensitivity to negative reinforcement learning, consistently connecting contextual information with negative associations over time, a biochemical imbalance can, directly strengthen prior expectations through long-term potentiation (LTP) [8,30,31].

Microbial Dysbiosis and the Emergence of Anxiety

Chronic inflammation of the intestine is associated with environmentally acquired microbial dysbiosis, for example, from a food allergy. The possibility of anxiety states and trait anxiety may result from intestinal microbial dysbiosis in several ways (**Figure 1**) [8,10]. Environmental change in the gut with an aversive component that was previously unrecognized (E>X) results in the adjustment of old concepts or the generation of new concepts [8]. Learned responses lead to the interoceptive autonomic reflexes and aversive components being integrated into the concept and the prediction error minimization strategies updated [8]. The interoceptive autonomic reflexes consist of an immediate immunological response to the intruder, which leads to a temporary change of physiological state, including an inflammatory response [32]. The subsequent responses and their symptoms induce psychological changes, possibly manifested as a perceived state of anxiety [33,34]. These anxiety states are then maintained and fostered by the inflammatory changes in the intestinal environment and the microbiota, with a change in the mucosal pH, nutrient availability, and host immunity [35].

Therefore, following repeated gastrointestinal inflammation episodes, the same interoceptive response of distress and anxiety may become an internally learned concept [33,35]. However, with little or no conscious awareness of an actual cause, this physiologically learned concept might become increased over time by the reoccurring detection of specific gastrointestinal stressors and associated prediction error minimization responses, leading to spatiotemporally increased outbursts of presumably arbitrary anxiety states [33,35]. An overgeneralized negative association to non-specific sensory stimuli may result in ongoing subliminal anxiety, such as trait anxiety (E<X) (**Figure 1**) [8].

In the gut's internal milieu, constant chronic inflammation can lead to a change in the readiness potential to increase predictability by preparing for the most expected error cause to match the prior prediction [36]. Therefore, an increase in the production of antibodies, free reactive compounds such as histamine, and down-regulation of inactivating enzymes such as diamine oxidase, may eventually occur [32]. Inflammation of the gastrointestinal tract affects microbial symbiosis, and may induce long-term neuromodulatory changes through microbial signaling [10,35,37,38]. The resulting unfavorable endocrine and neurochemical conditions may become chronic.

Maintenance of Anxiety Due to Altered Gut-Brain Interactions

In 2017, Van de Cruys proposed that it was not prediction error minimization alone that resulted in chronic effects such as trait anxiety, but that a negative predictive dynamic occurs over time with uncertainty regarding resolution [11]. This previously described concept completes the current model (**Figure 1**) [8,11]. As a result of overgeneralizing non-aversive concepts to a negative effect, the individual may increasingly detect incongruence between salient sensory signals and generated concept-responses [11]. This decrease in sensory predictability results in perceptual instability due to stronger weighted concept bias to implement prediction error minimization or active interoceptive inference [11]. When the brain detects contradicting responses to well-established higher-order, multimodal concepts, the brain experiences negative surprise instead of reward [11,39], these effects will re-adjust the internal model according to the reoccurring prediction error (E≥X) [39]. It may be hypothesized that this can lead to the brain generating a variety of prior expectations (X, X+1, X+2, X+3) according to indistinguishably similar sensory causes (E, E+1, E+2) [8,11]. These effects may alter the dynamics and confidence of prediction error minimization in a negative way, with an altered

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dynamic that may result in general uncertainty to maintain the agent in a continuous state of anxiety (E>X>E) [8,11]. General factors that can affect the reward-cost response and probability of successful prediction error minimization include environmental aversions, the individual's cognitive strategies, or their biological predisposition for unfavorable physiological or biochemical conditions [11]. For example, a biochemical imbalance may alter precision-weighing and sensory filtering by increasing sensitivity to the more salient incoming signals [8,15,31,40]. Therefore, the result may be sensory recognition uncertainty and general anxiety [8,15,31,40-42].

Maintenance of Anxiety Due to Gut Microbial Dysbiosis

The maintenance of anxiety due to gut microbial dysbiosis may be proposed due to the effects of chronic inflammation due to factors such as food allergens and the results of maintained perceptual uncertainty. Due to the heightened threat expectations and readiness for environmental stressors, the persistent triggers of inflammation may result in activation of the immune system without justifiable cause (E<X) [35,36]. The overgeneralization of an immune response that includes antibody binding and interoceptive response, or an aversion-based immune reaction, might increase interoceptive uncertainty through the conceptualized prediction error minimization response [35,36]. Therefore, when a heightened threat expectation is repeatedly not confirmed, the internal model will try to modulate and adjust according to the salient and unmatched sensory evidence (E≥X) [8,11]. However, due to unawareness of gastrointestinal aversion, such as a food allergen, and inconsistent and unpredictable stress exposure, a build-up of inflammatory mediators may negatively affect intestinal regulation and immune function [10,43]. A negative dynamic and low confidence of successful prediction error minimization may result, with consistent uncertainty across an increasing number of contextually different concepts on a multimodal processing-level (E>X>E) [8,11]. These arbitrary aversive interoceptive responses to inconsistent causes lead to suboptimal functioning due to increased energy use and altered homeostasis, maintaining the body in an anxious state, which in turn can be understood as trait anxiety [5,7,43].

This perceptual inaccuracy dynamic can be further strengthened through dysbiotic microbial signaling, directly modulating the functional connectivity of involved brain networks [43,44]. Therefore, manipulating neurochemistry and pro-inflammatory cytokines is merely one pathway, as a diseased gut can alter cognitive and physical functioning in a bi-directional manner [10,44]. Therefore, it may be possible to understand how the proposed cognitive and physiological model directly and indirectly affects interoception, trait anxiety, and the gut microbiome.

Future Recommendations: A Cognitive and Physiological Model of Interoception, Trait Anxiety, and the Gut Microbiome

In this review, a cognitive and physiological model has been proposed and discussed that may lead to a predictive model for the interaction between interoception, trait anxiety, and the gut microbiome. A hierarchy of consecutive processes has been suggested that lead to trait anxiety. A distinction has been made between the emergence of anxiety states and their manifestation and subsequent maintenance of trait anxiety. The basis for the model is the recurrent experience of negative anxiety states that become internalized. When these anxiety states cannot be directly linked to an aversive event, associations are constructed with other, non-aversive components of higher-order concepts [20]. This may cause overgeneralization of negative interoceptive responses to neutral sensory stimuli [8]. This cross-manifestation then becomes more stable and pronounced across a wide distribution of conceptual components, giving rise to regular, seemingly arbitrary, prediction error minimization in the form of anxiety evoking active interoceptive responses, leading to perceived anxiety [8,11].

Consequently, the aversive overgeneralization of sensory evidence results in an interoceptive anxiety response that repeatedly turns out to be incongruous with the actual sensory cause [8]. The result of overgeneralization is that the brain is forced to adapt the aversive concept to salient and incongruent error components by generating more fine-grained or slightly different concepts [8]. Since prediction generation is subject to uncertainty, due to the close similarity of sensory causes, associated concepts, and indeterminate responses, the confidence in successful prediction error minimization decreases [8]. Therefore, the constant change in the success rate results in a negative dynamic, increasing predictive uncertainty and reducing the individual's confidence to act, maintaining trait anxiety [11,29].

Whether this uncertainty is reinforced, possibly to the extent where it manifests as a mental health disorder, depends on several factors, including the individual's cognitive appraisal strategy. For example, where negative cognitive appraisal, such as situational avoidance, can reciprocally reinforce the overgeneralization of anxious experiences, positive appraisal could facilitate its gradual extinction [3,40,45,46].

Therefore, we believe that an integrative model of trait anxiety, as described in this review, may facilitate the understanding of underlying mechanisms involved in trait anxiety and support new approaches to appropriate treatment strategies. By breaking the positive feedback loop that continuously reinforces negative behavior associated with threat confirmation and neuronal strengthening of the fear response, trait anxiety could be treated at its source and individualized for each

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patient. For example, a cognitive approach or medical intervention may be beneficial for some patients with trait anxiety, and simple exclusion of an aversive component may benefit other patients [47]. The model described in this review supports that a thorough evaluation of the underlying cause of the anxiety response is the basis of individualized treatment [47]. For example, regarding the gut microbiome, removing the physiological cause, such as a food allergen, should be the first step in treatment [47]. This type of treatment approach would reduce gut inflammation, restore normal intestinal flora, reduce the production of inflammatory mediators, antibodies, and reactive compounds [36]. Also, when the model's predictability and reliability are improved due to increased awareness of the individual's nutritional needs, the internal model will adjust to the heightened interoceptive and exteroceptive stability over time. Future accidental exposure to environmental aversions, such as food allergens, should only result in an appropriate interoceptive response and a temporary anxiety state rather than an anxiety trait. Individualized probiotic treatment may also be considered when gut allergens are not identified in patients with trait anxiety.

It must be acknowledged that a limitation to any hypothesis or potential predictive model is that it requires validation by real-world evaluation. This hypothesis has been developed mainly using a cognitive approach. However, the model's implementation will require a multidisciplinary approach that includes psychiatrists, physicians, gastroenterologists, and microbiologists. Therefore, further development of this or similar models is recommended with emphasis on gastrointestinal aversion. By studying how chemical signaling of specific bacteria can alter functional connectivity of specified brain regions, it may be possible to understand and possibly alter the generation of perception. The effects of controlling microbial dysbiosis could be a potential in vivo approach to further investigate gut-brain communication and the gut microbiota's effects on human cognition and behavior.

Conclusions

This review has proposed and outlined a predictive model to explain the emergence, manifestations, and maintenance of trait anxiety using gut microbial dysbiosis or imbalance of the gut microbiome. The proposed model has assumed that anxiety states arise from active interoceptive inference and that the subsequent activation of autonomic responses results from aversive sensory encounters. Any hypothesis-based predictive model requires testing in the real world, but it is hoped that the development of this model will stimulate further studies and the development of individualized approaches to the evaluation and management of patients with anxiety disorders that include trait anxiety.

Conflict of Interest

None.

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