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# Regulation of Functions of the Brain and Body by the Principle of Predictive Coding: Implications for Impairments of the Brain-Gut Axis

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#### Abstract

Lisa Feldman-Barrett, who has promoted a psychological constructivism theory of affect, recently proposed the Embodied Predictive Interoception Coding (EPIC) model of affect, based on the perspective of predictive coding. The theoretical framework of predictive coding argues that the brain creates inner models that can provide predictions for perception and motor movement, and that perception and behaviors emerge from Bayesian computations rooted in these predictions. The EPIC model expands this framework to interoception, which is perception of the inner body, and tries to explain the phenomena of affect as integrative experiences based on interoception. This perspective provides important implications for understanding issues of the brain–gut axis and its impairments.

Keywords: interoception, predictive coding, brain-gut axis

#### Introduction

The brain and gut have a tight and bidirectional functional association (Camilleri & Di Lorenzo, 2012). This is not surprising, considering that the neural system and the brain have been developed for effective regulation of digestive organs over the history of evolution. Thus, functional gastrointestinal diseases, such as irritable bowel syndrome (IBS), must be understood as impairments of the brain–gut functional association, and not as illnesses of only local sites in the intestines.

The Embodied Predictive Interoception Coding (EPIC) model, which was proposed by Lisa Feldman-Barrett, a theorist arguing psychological constructivism of emotion (Feldman-Barrett, 2017; Feldman-Barrett, Quigley, & Hamilton, 2016; Feldman-Barrett & Simmons, 2015) can provide a useful theoretical framework to understand the issues of brain–gut functional association. The EPIC model is based on the concept of predictive coding, which hypothesizes that the brain constructs inner models in various functional layers, and that every function of the brain emerges from computations of the models and input signals. The EPIC model further

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hypothesizes that all mental functions, such as perception, motor, cognition, and affect, can be uniformly explained by this concept. The EPIC model has not been completed as a systematic theory, and empirical verification of the EPIC model is difficult. Thus, the EPIC model is considered a meta-theory.

However, the EPIC model is attractive because we can draw many implications about the association of the brain and body, and can develop many hypotheses that can be examined empirically. This article first introduces the EPIC model, and second argues implications of this model for issues of brain–gut functional association and its impairments.

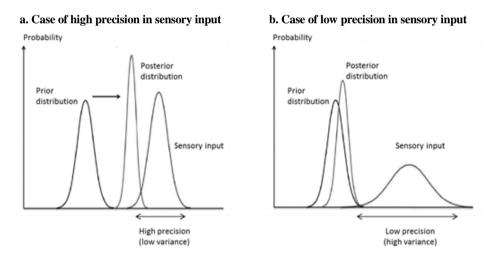
# **Predictive Coding**

The brain is not a passive organ that solely responds to input signals from sensory organs, but actively constructs perception based on inner models predicting future input signals, and on computations of differences between the predictions and input signals (prediction error). Such a principle of functions of the brain is called "predictive coding" (Friston, 2010; Friston, Kilner, & Harrison, 2006). The origin of this concept can be traced back to the unconscious inference of vision, which was proposed by Helmholtz, a physicist in the 19<sup>th</sup> century (Helmholtz, 1866/1962). Human vision has many limitations; for example, visual images are not clear except within the narrow range of the central vision, and the blind spot and vessels in the surface of the retina interfere with clear vision. Nevertheless, we have stable and clear visual experiences. Helmholtz proposed that this is because we create images of the external world by making inferences from limited visual signals, based on past experiences. As such, inferences are instantly conducted without awareness. Helmholtz called the process "unconscious inference."

In the theory of predictive coding, such processes of perception in the brain are explained as an analogy of the principle of Bayesian statistics (Figure 1; Ainley, Apps, Fotopoulou, & Tsakiris, 2016). A prediction of perception by an inner model is represented as a probabilistic distribution. This corresponds to the prior distribution in Bayesian statistics. Sensory input can also be represented as a probabilistic distribution error is computed as the difference between the distributions of the prediction and sensory input. This sensory input corresponds to observation or likelihood in Bayesian statistics, and then the posterior distribution is computed based on updating in the theorem of Bayes. Our subjective experiences of perception can be considered as awareness of the computational processes of the posterior distribution based on the prior distribution and sensory input. In this framework, the prediction refers to patterns of spontaneous activity in neural networks in the brain. Thus, it should be noted that the prediction is a purely biological phenomenon, and not the result of mental activity or meaning caused by intention.

One of the important factors determining experiences of perception is precision of the prediction and sensory input. Precision refers to the variance of a probabilistic distribution, and is represented in the width of the distribution (Figure 1). Precision of an inner model is higher for an event experienced frequently, and lower for an event that is rarely encountered. However, paying attention to a target increases precision of the sensory input. Given a distance between the means of the prediction and sensory input, a subjective experience will be about centered between the prediction and sensory input when precisions of the prediction and sensory input are the same levels (Figure 1a). When precision of the prediction is high and precision of sensory input is low, a subjective experience will be almost completely dependent on the prediction, and will appear very different from the real sensory input (Figure 1b). In addition, higher precisions of the prior and posterior distributions will result in a clearer experience of the perception.

It is thought that such Bayesian computations are involved in processing in every modality of perception and motor function. Such computations are hierarchically conducted from the lowest level in sensory organs (e.g. signal processing in the retina) to the highest level in associative areas (e.g. goal-directed processing in the prefrontal cortex). Organisms, including humans, construct and maintain integrated and consistent images of self and the world by minimizing the sum of the prediction error detected in such hierarchical computations. This sum of the prediction error is called the "free energy", as an analogy of the theory of thermodynamics (Friston, 2010; Friston et al., 2006). To minimize the prediction



*Figure 1.* The principle of predictive coding (Ainley et al., 2016). The prior distribution represents a prediction for perception, which is produced by an inner model. Once a sensory signal is received, a prediction error, which is the difference between the prediction and sensory input, is computed. Based on the theorem of Bayes, the prior distribution is updated to the posterior distribution. It is thought that a subjective experience of perception emerges from this series of processes. In (a) and (b), the prediction is same, and the prediction error (distance between means of the prediction and sensory signal) is also same. However, the precision of the sensory signal is lower in b than in a. When the precision of the sensory input is low, the subjective experience of perception is almost completely determined by the prediction, independent from the actual sensory input (b).

error, the organism will either update the inner model or actively modulate the sensory input by changing behaviors. The former process is similar to the unconscious inference by Helmholtz, and the latter process is called "active inference." Examples of active inference include changing the distance or the visual angle to modulate vision by moving the body, or paying attention to and gazing at a target. Organisms dynamically use both of these methods to reduce the sum of the prediction error. This is thought of as the basic principle of the brain, and is called "the principle of free energy". Although this theory remains hypothetical, it is gaining attention in cognitive neuroscience research fields.

### **Predictive Coding of Interoception**

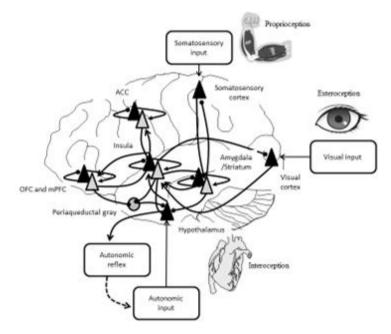
Feldman-Barrett and her colleagues have proposed that in addition to exteroception (e.g. vision and hearing) and proprioception (perception of the location of the body and bodily movement), interoception, which is perception of the inner body such as inner organs and vessels, is established by the principle of predictive coding (Ainley et al., 2016; Feldman-Barrett et al., 2016; Feldman-Barrett & Simmons, 2015; Seth & Friston, 2016). Organisms have to appropriately regulate bodily states to maintain homeostasis. To achieve this, the brain represents the body's current state and its desirable state (goal), and constructs the inner model of the body to satisfy the goals of the body. The model determines desirable ranges of states, including blood pressure, blood glucose level, concentration of hormones, and concentration of cytokines related to immune functions, depending on specific situations. When the body receives input signals, the signals are compared with predictions by the inner model, and the differences between them are computed as prediction errors. Organisms regulate their bodily states to minimize the prediction errors. To reduce prediction errors, an organism both updates the inner model and alters its bodily states.

Importantly, sensations of the inner body that are subjectively experienced are thought of as awareness of computational processing of the posterior probabilistic distribution of the bodily state from the prior distribution, and sensory input from the body. For example, peristaltic motion of the intestines is rarely consciously felt. This is because the prediction error between the prediction of the motion and the actual motion in the intestines is small. However, inflammation in the intestines caused by infection will increase the prediction error, which is then perceived as discomfort and pain in the intestines. Furthermore, in such a situation, precision of sensory signals from the intestines will increase by paying attention to the intestines, and perception of the intestines will become more sensitive. As a result, one can be conscious of even tiny movements of the intestines, sometimes perceived as pain. In this case, a person may stroke and press the abdomen to confirm the discomfort and to reduce the pain, and these actions are interpreted as attempts to minimize the prediction errors by active inference.

One of the critical brain regions for predictive coding of interoception is the insula. The insula is a cortical region located in the temporal lobe, and receives signals from all parts of the body. The anterior portion of the insula is composed of

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agranular cortex, and the posterior portion is granular cortex, which receives bodily signals. In addition, the posterior insula has dense neural projections from agranular cortices of the medial prefrontal cortex (mPFC) and orbitofrontal cortex (OFC). These anatomical characteristics suggest that the anterior insula, and the mPFC and OFC, might construct the inner models of the body, and that prediction errors might be computed in the posterior insula (Feldman-Barrett, 2017; Feldman-Barrett et al., 2016; Feldman-Barrett & Simmons, 2015). Furthermore, the amygdala, striatum and anterior cingulate cortex (ACC) also play important roles in adjusting computations of the predictions and predictions errors, and in linking such parameters with behaviors. In sum, these brain areas might work as hubs in the neural network for computations of predictive coding to optimally regulate functions of the brain and body in certain situations (Figure 2).



*Figure 2*. Neural mechanisms of predictive coding (adapted from Seth & Friston, 2016). Triangles in the figure represent groups of pyramidal neurons. Gray triangles are neurons computing predictions, and black triangles are neurons computing prediction errors. The insula, orbitofrontal cortex (OFC) and medial prefrontal cortex (mPFC), anterior cingulate cortex (ACC), and amygdala/striatum, which include both neurons computing predictions and prediction errors, are hub regions of predictive coding. Sensory areas, such as the visual area and somatosensory area, are granular cortices, and are involved in the input of sensory signals and computation of prediction errors. The area of the periaqueductal gray modulates the precision of interoceptive signals.

# Functional Association among Brain, Body, and Behavior Based on Predictive Coding

The principle of predictive coding and the EPIC model can provide interesting and useful explanations for empirical findings about functional associations among brain activity, bodily responses, and behaviors, depending on demands from different environments. Here, we examine findings from our laboratory on the basis of the EPIC model.

#### Contingency between Stimulus and Outcome and Activities of Brain and Body

We have examined how behaviors, brain activity, and physiological responses, including those of the autonomic, endocrine, and immune systems, are shaped by assessing contingencies between stimuli and outcomes (Kimura, Ohira, Isowa, Matsunaga, & Murashima, 2007; Ohira et al., 2009, 2010). In these studies, a gambling task called the stochastic learning task was used. In each trial of this task, human participants choose one of two options to gain monetary reward and to avoid monetary loss. One option is more advantageous because the option leads to reward at a higher probability. The other option is more disadvantageous because the probability of getting a reward is lower.

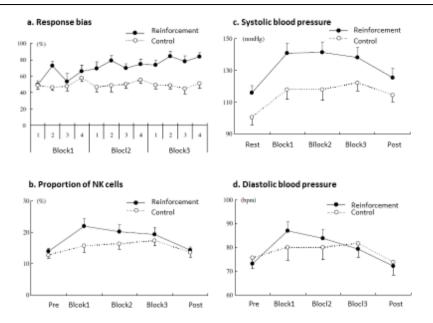
Behavioral characteristics of this task are well represented by a computational model called reinforcement learning (Lee, Seo, & Jung, 2012). One of the typical algorithms of reinforcement learning, Q learning, is represented as follows:

$$Q_{(a(t+1))}(t+1) = Q_{a(t)}(t) + \propto \left( R(t+1) - Q_{a(t)}(t) \right), \quad (1)$$
$$P(a(t)) = \frac{1}{1 + \exp[-\beta(Q_a(t) - Q_b(t))]}. \quad (2)$$

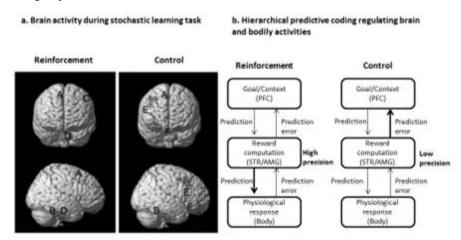
Here,  $Q_{i(t)}(t)$  in equation (1) represents values of two options, i = a or b, at time point, t. This variable corresponds to the predictions about reward delivered by the options, computed by the inner model. If the choice of option a at the next time point can provide reward R(t+1), the difference between the reward and the prediction of the value  $Q_{a(t)}(t)$  is the prediction error, represented as  $R(t+1) - Q_{a(t)}(t)$  in equation (1). The value is then updated to minimize this prediction error. A positive score of the prediction error means a better outcome compared with the prediction, thus the value of the option will be increased. A negative score of the prediction error means a worse outcome compared with the prediction, thus the value of the option is decreased. In this way, the values of the two options are continuously updated, and based on the values, a probability of choice of option a at time point t can be represented as a function described in equation (2). Updating of values described in equation (1) is thought to occur in a region of the ventral striatum called the nucleus accumbens. Choices based on the values are thought to be conducted in a neural network including the dorsal striatum and the ACC (Lee et al., 2012). Thus, computations by predictive coding regarding values of options are completed mainly in the striatum during this task.

We used two experimental groups in this task (Kimura et al., 2007); in one group, one option was linked with monetary reward at a probability of 70%, and the other option was linked with reward at 30% (Reinforcement). In the other group, reward for a participant was delivered with the matched timing to a paired participant in the Reinforcement group, but was unrelated to the choices by the participant (Control). Importantly, the total volume and delivery timing of the reward were the same between the two participants in both groups. However, the participant in the Reinforcement group was able to learn the contingencies between the options and outcomes, whereas the participant in the Control group was not. Psychologically, this is called a yoked paradigm. In the Reinforcement group, it is thought that a large prediction error for reward occurs at the beginning of the task, and the prediction error remains large in the Control group.

The response bias (rate of choice for the advantageous option) in the Reinforcement group converged at about 80%, through a typical learning curve (Figure 3a). The response bias in the Control group remained at about 50% through the end of the task, suggesting that the participants in the Control group continued efforts to search for contingencies between options and outcomes. Interestingly, physiological responses showed clear differentiations between the two groups. The Reinforcement group consistently indicated stronger responses in immune (proportion of natural killer cells; Figure 3b) and autonomic [systolic blood pressure (Figure 3c) and diastolic blood pressure (Figure 3d)] responses, whereas the physiological responses were remarkably suppressed in the Control group. Such a differentiation of physiological responses depending on the contingencies between stimuli and outcomes in a similar behavioral task has been robustly replicated in another study (Ohira et al., 2009). During the task, brain activation was observed in the ACC, OFC, and striatum (Figure 4; Ohira et al., 2009, 2010), which are the hub regions of predictive coding described in Figure 2. In addition, the activation was more dominant in the Control group compared with the Reinforcement group, suggesting that physiological responses decreased in the Control group not because they abandoned efforts for learning, but because they continued efforts to reduce the reward prediction error.



*Figure 3.* Changes of response bias, proportion of natural killer (NK) cells in peripheral blood, and blood pressure, during the stochastic learning task (Kimura et al., 2007). (a) In the Reinforcement learning group, the rate of choices of the advantageous option (response bias) gradually increased. In the Control group, the rate of choice for both options remained almost equal at the end of the task. (b) In the Reinforcement group, proportions of NK cells in blood remarkably increased at the initiation of the task, and were maintained at a high level during the task. In the Control group, the change of NK cells was suppressed. Systolic blood pressure (c) and diastolic blood pressure (d) also showed the similar differentiated patterns between the two groups.



*Figure 4*. Brain and body activity during a stochastic learning task. (a) Brain activity measured by positron emission tomography during the stochastic learning task (Ohira et al., 2010). A:

anterior cingulate cortex, B: cerebellum, C: left dorsolateral prefrontal cortex, D: pons, E: right dorsolateral prefrontal cortex, F: orbitofrontal cortex. Activation in the striatum was also observed, especially in the Reinforcement group (not shown in the figure). (b) Schematic expression of hierarchical predictive coding. In the Reinforcement group, the precision of the model in reward computation increases, thus physiological responses in the body are strongly affected. In the Control group, the precision in the model of reward computation is maintained at a lower level, and continuous updating is conducted in the higher level of the brain. For the body, both sympathetic and parasympathetic influences are sent, the offset processing of which suppress physiological responses. PFC: prefrontal cortex. STR: striatum. AMG: amygdala.

These findings can be interpreted in the context of the EPIC model (Figure 4b). The reward system should be the core system in the hierarchical system of predictive coding. The reward system can affect the higher system that maintains goals and contexts (probably in the PFC), by providing signals of the reward prediction errors. Furthermore, the reward system can affect the lower system, which regulates bodily states, by providing signals of the predictions (Figure 5; Smith, Thayer, Khalsa, & Lane, 2017). In the Reinforcement group, computations for reward will rapidly converge, and precision of the inner model will improve, through sampling of the outcome in each trial. This signal reduces the prediction errors in models about goals and contexts in the higher system, resulting in the formation of stable strategies for coping. The computations for reward will also affect the lower system, and will alter bodily responses in a manner that is consistent with the prediction delivered from the reward system. In this case, the set point of the autonomic activity level will be upregulated to increase bodily activity for behaviors to get a reward. Such processes would cause increases in the activities of the autonomic and immune systems described in Figure 3. In the Control group, computations of reward do not converge, thus signals of the reward prediction error sent to the higher system remain large. As a result, higher inner models in the PFC areas continue to work at updating the models. Stronger activation of the PFC areas shown in Figure 4a might reflect such activity in the PFC. Simultaneously, in the lower system, signals facilitating activity of the sympathetic nervous system, to promote approach behaviors to get a reward, and signals facilitating activity of the parasympathetic nervous system, to promote avoidance behaviors to prevent loss, will be sent. As a result of contamination of these sympathetic and parasympathetic signals, physiological responses in the autonomic and immune systems will be suppressed. Indeed, the power of the high frequency component in heart rate variability (HRV), which is an index of activation of the parasympathetic nervous system, was remarkably elevated in the Control group (Ohira et al., 2010).

#### Responses to Change of Contingency: Heart Rate Variability as an Index Reflecting Precision of Inner Models

Both in natural environments and in social environments, the contingency between stimulus–behavior–outcome is not fixed, but alters as time passes. For example, it is not guaranteed that an animal can get food at the same place where it got food in the past. Or, a strategy to attract a female for an animal is not necessarily effective at the next opportunity. Organisms must change behaviors to follow such alterations of the contingency. This ability is called goal-directed action (Pezzulo, van der Meer, Lansink, & Pennartz, 2014).

Goal-directed action is a function that occurs at a higher level of predictive coding, and is thought to involve the PFC and dorsomedial striatum. From the perspective of the EPIC model, higher precision of the higher level inner model leads to stronger influences of prediction signals on lower system, and as a result, the ability to flexibly regulate behaviors and physiological responses will be more dominant (Pezzulo, Rigoli, & Friston, 2015; Smith et al., 2017). Smith et al. (2017) have argued that HRV is a good index of the precision of the inner models for goal-directed action occurring in the PFC areas. HRV is a measure of fluctuations in the intervals of heart beats. However, in addition to cardiac function, it is thought that HRV can be used as an index of the brain's ability to regulate various bodily states (Thayer, Ahs, Fredrikson, Sollers, & Wager, 2012).

To examine such a theoretical hypothesis, we observed the activity of the brain and several physiological responses while participants in groups with higher and lower tonic HRV levels performed a stochastic reversal learning task in which the stimulus-behavior-outcome contingency changes (Ohira et al., 2013). The stochastic reversal learning task is also a gambling task. In this task, an advantageous option and a disadvantageous option are suddenly reversed during the task, requiring participants to suppress previously dominant behaviors and re-learn a new contingency. The high HRV group consistently showed higher levels of reactivity in indices of autonomic, endocrine, and immune systems. Furthermore, activation in the OFC, ACC, insula, and striatum (hub regions of predictive coding; Figure 2) indicated significant correlations with the physiological indices. These results seem consistent with the hypothesis by Smith et al. (2017). Namely, the participants in the high HRV group can sensitively detect the change of contingency by the higher system for the goal-directed action, thus the higher system can effectively regulate various physiological responses by sending prediction signals with higher precision. In the low HRV group, both brain activity and physiological responses showed blunted reactivity to the change of contingency. It is suggested that participants in the low HRV might be less sensitive to the change of contingency, probably because their functioning of goal-directed action has declined.

The empirical findings described in this section seem to support the theoretical framework of the EPIC model. It has been suggested that the EPIC model is also useful to explain psychosomatic problems, such as issues of the brain–gut axis, and mechanisms of psychosomatic diseases.

#### Computational Psychosomatics: Implications for Issues of the Brain–Gut Axis

The concepts of predictive coding and the EPIC model have been expanded to psychosomatic medicine (Petzschner, Weber, Gard, & Stephan, 2017). Psychosomatic medicine is concerned with various somatic diseases that are caused or influenced by mental processes (Fava & Sonino, 2010). Applications of the computational models to psychosomatic medicine are still rare (but see de Berker et al., 2016; Fineberg, Steinfeld, Brewer, & Corlett, 2014). However, these can provide a unified explanation for the underlying mechanisms of different symptoms. As described above, important components of predictive coding are the prior distribution (prediction), sensory input, prediction error, and precision. Psychosomatic symptoms can be considered to be caused by impairments of these components.

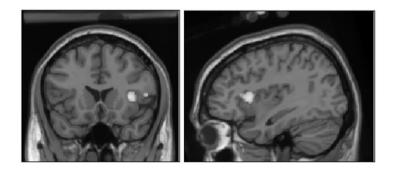
For example, depression is sometimes accompanied by somatic disorders such as cardiac, immunological, and metabolic disturbances (Joynt, Whallen, & O'Connor, 2003; Renn, Feiciano, & Segal, 2011). In the framework of the EPIC model, this can be explained as persistent effects of impaired high-level inner models predicting uncontrollability and uncertainty of environments with higher precisions (strong negative beliefs) on functions in allostatic control regions, such as the insula and ACC, or on autonomic effector regions, such as the hypothalamus and periaqueductal gray (Figure 2), leading to an allostatic load resulting in somatic disturbances. An alternative possibility is that depression is caused by a reaction to an initial somatic disease. Systemic inflammation mediated by increased proinflammatory cytokines, such as IL-6 and TNF- $\alpha$ , can affect brain functions and are linked with the onset of depression (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008). This might provide greater prediction errors in the above described allostatic control regions, leading to updating of the inner models in the negative direction, accompanied by hedonically negative affective states.

Another typical example of psychosomatic disease is the functional digestive disorder, IBS. The diagnosis of IBS is based on identification of the following symptoms in the Rome III criteria (Camilleri & Di Lorenzo, 2012): recurrent abdominal pain and discomfort for at least 3 days per month in the last 3 months, and no evidence of inflammatory, anatomic, metabolic, or neoplastic processes that explain the symptoms. In addition, three main determinants have been considered for IBS: psychosocial factors, altered motility, and altered sensation. Given no evidence of organic disturbances in IBS, it is assumed that the main cause of this disease is in impaired processes in the brain-gut axis. First, it is hypothesized that the abnormal inner models in the control regions of the intestines with high precision might continuously produce a perception related to pain and discomfort in the intestines, even though sensory signals from the intestines are normal. However, large prediction errors in states of the intestines between the predictions from the inner models in the brain and actual states of the intestine should be minimized following the principle of predictive coding. As precisions of the inner models are extremely high, one of the dominant ways to minimize the prediction error is alteration of motility of the intestine. In this way, the brain-driven abnormalities in the intestine in IBS result in alterations in defecation and in frequency and form of stool.

We conducted a neuroimaging study for IBS by using O<sup>15</sup>-PET (Kanazawa et al., 2007). In this study, a polyethylene balloon was inserted in the rectum of patients of IBS and healthy controls. The air pressure was gradually increased, and the participants in both groups evaluated subjective pain and discomfort during the task. Also, their brain activation was measured during the task by PET. As expected, compared with the normal controls, the IBS patients showed remarkably lower thresholds of air pressure that caused subjective pain for the physical stimulation of their rectum. More importantly, the anterior insula showed greater activation during the task in the IBS patients than in the normal controls (Figure 5). As no difference in brain activity between the IBS patients and normal controls was identified in the somatosensory areas, the reported sensitivity for stimulation of the rectum in the IBS patients does not appear to involve the bottom-up processes of the rectum. Rather, it is assumed that their enhanced sensitivity can be attributed to the top-down processes that are rooted in abnormal and highly precise inner models located in the anterior insula. The pain and discomfort in the rectum perceived by the IBS patients were real, however they were produced in their brains.

For diseases of the brain–gut axis, the following causes should be considered (Petzschner et al., 2017): (1) A real bodily source of dyshomeostasis in the intestines, (2) altered sensations in the intestines, (3) altered prediction caused by impaired inner models in the brain, or (4) inadequate control by the brain over autonomic, endocrine, and immunological responses, based on computations of predictions and prediction errors of sensations in the intestines.

This perspective could be used to produce hypotheses that can be empirically examined, and thus will be beneficial to identify specific causes of diseases and to develop effective treatments.



*Figure 5.* Activation of the right anterior insula (white circle) during stimulation of the rectum in patients of irritable bowel syndrome. Brain activation was shown by a subtraction analysis of patients of irritable bowel syndrome minus healthy controls (Kanazawa et al., 2007).

#### Conclusion

This article introduced basic concepts of predictive coding and the EPIC model as an expansion of predictive coding to interoception. Although these theoretical perspectives are still under debate for their validity, these models can provide unified explanations for many phenomena involving functional associations of the brain and body, accompanying a wide range of mental phenomena and behaviors, such as perception, cognition, affect, learning, and decision-making. This article also introduced examples of empirical data about the brain–body functional association, particularly that accompanying learning, and showed that those data can be explained by the theoretical perspectives of predictive coding and the EPIC model. Although the evidence described in this article is qualitative, quantitative verification of the hypothesized models for the brain–body functional association based on empirical data should be possible, for example using statistical modeling by the hierarchical Bayesian model (de Berker et al., 2016).

Furthermore, predictive coding and the EPIC model can be expanded to psychosomatic medicine, and disorders of the brain–gut axis provide good examples of such an expansion. Causes of disturbances in the function of the brain–gut axis, such as IBS, can be classified and examined in detail by applying the theoretical framework of predictive coding and the EPIC model. Such efforts will be beneficial to develop new effective treatments for diseases in the brain–gut axis.

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#### References

- Ainley, V., Apps, M. A. J., Fotopoulou, A., & Tsakiris, M. (2016). 'Bodily precision': A predictive coding account of individual differences in interoceptive accuracy. *Philosophical Transactions of the Royal Society B*, 371, 20160003. doi:doi.org/10. 1098/rstb.2016.0003
- Camilleri, M., & Di Lorenzo, C. (2012). The brain-gut axis: From basic understanding to treatment of irritable bowel syndrome and related disorders. *Journal of Pediatric Gastroenterology and Nutrition*, 54(4), 446-453.
- Dantzer, R., O'Connor, J. C., Freund, G. G., Johnson, R. W., & Kelley, K. W. (2008). From inflammation to sickness and depression: When the immune system subjugates the brain. *Nature Reviews Neuroscience*, 9, 46-56.

- de Berker, A. O., Rutledge, R. B., Mathys, C., Marshall, L., Cross, G. F., Dolan, R. J., & Bestmann, S. (2016). Computations of uncertainty mediate acute stress responses in humans. *Nature Communication*, 7, 10996. doi:10.1038/ncomms10996
- Fava, G. A., & Sonino, N. (2010). Psychosomatic medicine. International Journal of Clinical Practice, 64, 1155-1161.
- Feldman-Barrett, L. (2017). *How emotions are made: The secret life of the brain*. New York, NY: Houghton Mifflin Harcourt.
- Feldman-Barrett, L., Quigley, K. S., & Hamilton, P. (2016). An active inference theory of allostasis and interoception in depression. *Philosophical Transactions of the Royal Society B*, 371, 20160011. doi:doi.org/10.1098/rstb.2016.0011
- Feldman-Barrett, L., & Simmons, W. K. (2015). Interoceptive predictions in the brain. *Nature Review Neuroscience*, *16*, 419-429.
- Fineberg, S. K., Steinfeld, M., Brewer, J. A., & Corlett, P. R. (2014). A computational account of borderline personality disorder: Impaired predictive learning about self and others through bodily simulation. *Frontiers in Psychiatry*, 5, 111. doi:10.3389/fpsyt. 2014.00111
- Friston, K. (2010). The free-energy principle: A unified brain theory? *Nature Review Neuroscience*, *11*, 127-138.
- Friston, K., Kilner, J., & Harrison, L. (2006). A free energy principle for the brain. *Journal of Physiology Paris*, 100, 70-87.
- Helmholtz, H. (1866/1962). *Concerning the perceptions in general. Treatise on physiological optics. III* (3<sup>rd</sup> ed.). New York, NY: Dover.
- Joynt, K. E., Whallen, D. J., & O'Connor, C. M. (2003). Depression and cardiovascular disease: Mechanisms of interaction. *Biological Psychiatry*, 54, 248-261.
- Kanazawa, T., Konagaya, T., Imamura, H., Kanayama, N., Matsunaga, M., Ohira, H., Fukuyama, S., Shinoda, J., Nomura, M., Nogimori, T., Kaneko, H., & Kakamu, S. (2007). Study of brain-gut interaction in patients with irritable bowel syndrome. *Journal* of Aichi Medical University Association, 35, 59-70.
- Kimura, K., Ohira, H., Isowa, T., Matsunaga, M., & Murashima, S. (2007). Regulation of lymphocytes redistribution via autonomic nervous activity during stochastic learning. *Brain, Behavior, and Immunity*, 21, 921-934.
- Lee, D., Seo, H., & Jung, M. W. (2012). Neural basis of reinforcement learning and decision making. Annual Review of Neuroscience, 35, 287-308.
- Ohira, H., Fukuyama, S., Kimura, K., Nomura, M., Isowa, T., Ichikawa, N., ... Yamada, J. (2009). Regulation of natural killer cell redistribution by prefrontal cortex during stochastic learning. *NeuroImage*, 47, 897-907.
- Ohira, H., Ichikawa, N., Nomura, M., Isowa, T., Kimura, K., Kanayama, N., ... Yamada, J. (2010). Brain and autonomic association accompanying stochastic decision-making. *NeuroImage*, 49, 1024-1037.

- Ohira, H., Matsunaga, M., Osumi, T., Fukuyama, S., Shinoda, J., Yamada, J., & Gidron, Y. (2013). Vagal nerve activity as a moderator of brain-immune relationships. *Journal of Neuroimmunology*, 260, 28-36.
- Petzschner, F. H., Weber, L. A. E., Gard, T., & Stephan, K. E. (2017). Computational psychosomatics and computational psychiatry: Toward a joint framework for differential diagnosis. *Biological Psychiatry*, 82, 421-430.
- Pezzulo, G., Rigoli, F., & Friston, K. (2015). Active Inference, homeostatic regulation and adaptive behavioural control. *Progress in Neurobiology*, 134, 17-35.
- Pezzulo, G., van der Meer, M. A., Lansink, C. S., & Pennartz, C. M. (2014). Internally generated sequences in learning and executing goal-directed behavior. *Trends in Cognitive Sciences*, 18, 647-657.
- Renn, B. N., Feiciano, L., & Segal, D. L. (2011). The bidirectional relationship of depression and diabetes: A systematic review. *Clinical Psychological Review*, *31*, 1239-1246.
- Seth, A., & Friston, K. J. (2016). Active interoceptive inference and the emotional brain. *Philosophical Transactions of the Royal Society B*, 371, 20160007. doi:10.1098/rstb. 2016.0007
- Smith, R., Thayer, J. F., Khalsa, S. S., & Lane, R. D. (2017). The hierarchical basis of neurovisceral integration. *Neuroscience and Biobehavioral Reviews*, 75, 274-296.
- Thayer, J., Ahs, F., Fredrikson, M., Sollers, J. J., & Wager, T. D. (2012). A meta-analysis of heart rate variability and neuroimaging studies: Implications for heart rate variability as a marker of stress and health. *Neuroscience and Biobehavioral Review*, *36*, 747-756.

# Regulación de funciones del cerebro y el cuerpo según el principio de codificación predictiva: Implicaciones para la discapacidad del eje cerebro-intestino

#### Resumen

Lisa Feldman-Barrett, que promovió la teoría constructivista del afecto, recientemente ha propuesto el modelo de afecto la Codificación predictiva incorporada de la interocepción (EPIC), basado en la perspectiva de la codificación predictiva. El marco teórico de la codificación predictiva discute los hechos de que el cerebro crea modelos internos que puedan facilitar predicciones para la percepción y las habilidades motoras, y de que la percepción y la conducta surgen de los cálculos bayesianos que se basan en estas predicciones. El modelo EPIC expande este marco a la interocepción – la percepción del cuerpo interno, y trata de explicar el fenómeno de afecto como experiencia integrativa basada en la interocepción. Esta perspectiva ofrece implicaciones importantes para entender los problemas del eje cerebro-intestino y sus discapacidades.

Palabras clave: interocepción, codificación predictiva, eje cerebro-intestino

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