Don't Trust Your Gut: Interoceptive Dysregulation in Depression

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Evolutionary theory indicates that anxiety and depression may be caused by dysregulated neural processes involved in maintaining homeostasis. Experimental research suggests that emotional states are mediated by cortical areas devoted to processing interoception, defined as the brain's representation of internal physiological conditions. Lack of sufficient physical activity and decreased exposure to nature may result in interoceptive dysregulation. This paradigm reveals several emerging treatments of depression, including vagal nerve stimulation and mindfulness training. The connection between depression and impaired interoception may result from a modern lifestyle to which humans are not adequately adapted.

***Keywords*: Depression, Interoception, Insula, Evolution, Vagal nerve stimulation**

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Depression, the fourth leading cause of disability worldwide, affects psychological well-being by impairing social and emotional functioning (Liu et al., 2016). Depression is characterized by depressed mood and markedly diminished interest or pleasure in activities throughout the day, nearly every day (American Psychiatric Association, 2013). Depression can also involve significant weight loss, fatigue, diminished ability to concentrate and recurrent thoughts of death (APA, 2013).

As the single most common mental disorder in the United States, national surveys show that 16–17% of U.S. adults and 11–12% of adolescents have experienced a major depressive episode at least once (McLaughlin, 2011). This disorder involves significant impairment across numerous areas of functioning and is associated with increased risk of hospitalization, suicide, unemployment and need for medical care (McLaughlin, 2011).

Due to its widespread societal and economic costs, depression is a public health issue requiring further research into its etiology. Recent clinical breakthroughs have opened new doors into the treatment of depression, but a comprehensive evolutionary framework is currently lacking. In this paper I first propose a hypothesis pertaining to the neuroevolutionary basis of emotion and how the modern lifestyle may result in impaired interoception. I then proceed to review recent literature relating to (1) the neurological correlates of interoception, (2) the role of the vagus nerve in depression and (3) the neural mechanism of mindfulness-based treatment for depression.

Background

Emotion evolved from homeostatic control mechanisms in the brain

Depression is a disorder characterized by poorly calibrated motivational and emotional states; thus, further understanding of depression requires insight into the nature and evolution of emotion.

Recent scholarship has revealed a link between emotion and homeostasis, suggesting that the brain evolved principally to maintain metabolism and energy regulation (Barret et al., 2016). Emotional brain centers therefore utilize common neurological circuitry adapted toward maintenance of homeostasis and metabolism. The brain evolved to anticipate bodily needs and modulate energy regulation accordingly, thereby satisfying metabolic needs as required (Barret et al., 2016).

For example, the brain anticipates the onset of dehydration and adjusts blood pressure, urinary output and blood osmolality accordingly (Kandel et al., 2013). At the same time the brain activates a motivational state (thirst) to promote drinking. These homeostatic drives are predicted in advance of actual debilitation by dehydration such that an organism remains metabolically capable of seeking out water despite feeling thirsty.

Motivational states are key features of homeostatic control mechanisms. Fear can be viewed as a motivational state that results in survival-promoting activity. The brain predicts threats and prepares to act to confront or avoid these threats by freezing or initiating rapid movement. Both behaviors require redistribution of blood flow and changes in cardiac output and respiration (Barret et al., 2016). Fear and other emotions are intricately related to homeostatic drives and we suggest that emotions evolved as adaptations, or fine-tunings, of preexisting homeostatic circuitry (Barret & Simmons, 2015; Barret et al., 2016).

This evolutionary history means that human emotion invokes homeostatic changes even in sometimes inappropriate circumstances. As an example, the sight of a supervisor approaching an employee's desk might immediately invoke fear in the employee and therefore result in heightened heart rate, respiration and sweating. These rapid autonomic responses result from predicted metabolic needs in response to danger, and

although unhelpful in an office context, such neural predictions are logical from an evolutionary perspective.

Depression is a disease of interoception

Homeostatic regulation of emotional states results in changes in the body's internal systems including the immune, endocrine, and autonomic nervous systems (Barret et al., 2016). The perception of these changes is experienced as interoception, which refers to the perception of the physiological conditions of the body. Interoception is critical for homeostasis as it allows the brain to recognize current bodily conditions as well as coordinate allostatic changes to homeostatic parameters.

A key idea in this paper is that interoceptive sensations are experienced as low-level components of emotional and motivational states (Barret et al., 2016; Craig, A., 2002). This interoceptive dimension of emotion is provided by afferent connections (notably the vagus nerve) which deliver interoceptive input to brain regions involved in the mediation of emotion (Strigo et al., 2016). Thus, the common belief that emotion involves "gut feelings" may be physiologically accurate.

I propose that depression is a result of interoceptive dysregulation. Interoceptive dysregulation may arise from poorly calibrated interoceptive brain areas or from the improper relaying of bodily sensation. In this way, interoceptive dysregulation results in inaccurate "gut feelings" representing the body's internal state. These misinterpreted interoceptive sensations may manifest themselves as a persistent sense of diminished pleasure, low motivation, apathy, and overall negative emotion, all of which characterize depression.

Interoceptive dysregulation may result from a modern lifestyle

This state of interoceptive dysregulation may result from a modern sedentary lifestyle to which humans are not well adapted. This lifestyle is characterized by a lack of exercise and insufficient exposure to sunlight; both factors are associated with homeostatic control systems in the brain.

Insufficient light exposure

Lack of sunlight is closely correlated with depression. One study compared Brazilian equatorial workers to Swedish miners in the Arctic; results showed that equatorial workers reporting frequent sun exposure were significantly less likely to be depressed compared to the arctic group, despite reporting less work satisfaction, more work hours, and less sleep (Marqueze et al., 2015). This reduction in depression is significantly correlated with increases in sunlight exposure. Seasonal affective disorder, closely associated with depression, is also explained by seasonal changes in sunlight (Roecklein & Rohan, 2005).

A homeostatic paradigm may help explain the association of lack of sunlight and depression because light is directly involved in maintaining circadian rhythm. A vast array of homeostatic processes are under control of the suprachiasmatic nucleus (SCN) in the anterior hypothalamus. This nucleus is light-sensitive and regulates most circadian rhythms in the body (Kandel et al., 2013). Several studies have linked unusual SCN activity to depression and diurnal mood variation (Germain & Kupfer, 2008).

I suggest that lack of sufficient light exposure will result in defective circadian regulation by the SCN, resulting in homeostatic disequilibrium and corresponding changes in interoceptive signaling. These interoceptive signals indicate to the brain the physiological conditions resulting from aberrant homeostasis. My hypothesis predicts that these interoceptive sensations trigger the persistent negative affect characteristic of depression.

Sedentary activity and depression

It has long been known that depressed individuals are more likely to demonstrate a sedentary lifestyle. One study found that depressed individuals were approximately twice as likely to engage in highly sedentary behavior (Stubbs et al., 2018). Similarly, many studies have found that exercise is associated with positive clinical outcomes in depression. Follow-up examinations for individuals randomly prescribed either pharmacological antidepressants or exercise revealed that participants assigned exercise showed lower rates of depression relapse compared to the antidepressant group (Blumenthal et al., 1999). A subsequent study assigned participants to either group exercise, solitary exercise, or antidepressants; a reassessment one year later found that the only significant predictor of depression was lack of exercise (regardless of group exercise or solitary exercise). This means that individuals who reported regular exercise were the least likely to be depressed at the one-year follow-up (Babyak et al., 2000).

The efficacy of exercise as a treatment for depression is explained by interoceptive changes resulting from both adapted homeostasis and improved cardiorespiratory fitness. Indeed, exercise has resulted in beneficial adaption in homeostatic systems involved in stress response (Murri et al., 2019; Klaperski et al., 2014). This adapted homeostatic control of stress response may impact baseline autonomic stress indicators, including cardiac output and cortisol levels. We suggest that this exercise-induced adjustment of physiological parameters improves mood via changes in interoceptive signaling. Of particular note, exercise restores sympathovagal balance (a measure of autonomic nervous activity and vagus nerve traffic) and consequently improves autonomic control (Besnier et al., 2019; Murri et al., 2019).

Recalibration of sympathovagal balance as well as improved cardiorespiratory fitness itself may result in improved nervous coordination at the vagus nerve and enhanced representation of cardiorespiratory processes in the interoceptive sensory cortex (Gibson, J., 2019; Mehling et al., 2018). I believe that adaptive changes to neural architecture involved in interoception may stabilize mood in individuals with depression.

Previous research has shown that the modern lifestyle is far removed from the environment to which we are adapted (Freese et al., 2017). This mismatch may affect depression through a variety of mechanisms; we suggest here that interoception and sympathovagal balance is regulated by environmental variables such as light exposure, cardiovascular fitness and other homeostatic markers. The link between depression, cortical representation of interoception, and vagus nerve activity will now be discussed at length.

Neural correlates of interoceptive dysregulation

Interoception is the perception of feelings and sensations relating to the body's internal state. Such information is delivered to the brain through a variety of pathways, notably including the vagus nerve, a cranial nerve that innervates the heart, lungs and viscera. The vagus nerve delivers interoceptive information to the brainstem, neurons that ultimately project to other cortical areas involved in interoception (Strigo & Craig, 2016; Berthoud & Neuhuber, 2000).

Cortical regions receive, represent and integrate this interoceptive input. Among these regions, the insular and anterior cingulate cortices are most involved (Stern et al., 2017; Strigo & Craig, 2016; Strigo, 2002; Oppenheimer & Cechetto, 2016). Research shows that the insular and cingulate cortices constitute "the homeostatic sensorimotor cortex" and that these two adjacent regions are activated in humans "during all feelings and all emotions" (Strigo & Craig 2016, p. 2). Furthermore, clinical studies have found that loss of volume in the insula and anterior cingulate cortex is associated with a wide variety of mental disorders including depression and anxiety (Goodkind et al., 2015; Drevets et al., 2008).

Interoceptive cortex and depression

Evidence suggests that motivations arise from the anterior cingulate cortex, whereas feelings and affect originate from the insula (Strigo & Craig, 2016). It has been suggested that the insula imbues perceptions with emotional salience by gauging interoceptive stimuli and managing homeostatic and cardiovascular responses (Oppenheimer & Cechetto, 2016). Research shows that the right insula plays a role in fine-tuning sympathetic responses. Conversely, the left insula regulates parasympathetic activity (Tegeler et al., 2014; Strigo & Craig, 2016). Thus, hyperactivity of the right insula may result in some overactivation of the sympathetic nervous system.

A hyperactive right insula will regulate sympathetic responses, such as increases in blood flow to skeletal muscle, increased heart rate, hormonal changes, and heightened alertness. These physiological changes are delivered to the brain through the vagus nerve and other afferent pathways, and represented interoceptively in the insula. Our theory predicts that this sympathetic-associated interoception is interpreted as negative affect, such as stress, fear or sadness. Hypoactivity of the left insula (which regulates parasympathetic activity) will similarly result in negative affect. The following studies lend support to this theory.

Functional magnetic resonance imaging (fMRI) of patients with depression has indicated unusual interoceptive representation and functional organization in the insula (Avery et al., 2014) as well as other abnormalities in the anterior cingulate and insular cortices (Pandya et al., 2012). Neuroimaging techniques have shown that temporal asymmetry in the insula is associated with heart rate variability and that recalibration of bilateral insular activity correlates with reduction in depressive symptoms (Tegeler et al., 2014). Thus, deleterious changes to interoceptive functioning are indicated in depression. Evidence suggests that these changes to insular representation may result from impaired functioning of the vagus nerve which is responsible for mediating many interoceptive inputs (Strigo & Craig, 2016; Klarer et al., 2016). I will now address the vagus nerve and its role in depression.

Vagal nerve stimulation and interoception

Vagal nerve stimulation (VNS) is an increasingly recognized treatment for depression; it involves electrically stimulating the vagus nerve, usually transcutaneously by means of a stimulator unit applied on the surface of the ear. I suggest that the efficacy of VNS results from functional recalibration of interoceptive brain areas.

Research has established that vagal inputs activate the insular cortex in rats and monkeys (Strigo & Craig, 2016). Cardiorespiratory sensation has been particularly studied, and a direct projection of cardiorespiratory vagal activity to interoceptive cortex has been found (Strigo & Craig, 2016). Deafferentation of rodent models has further established that the vagus nerve modulates anxiety and fear (Klarer et al., 2014).

Recent neuroimaging findings have shown that vagal nerve stimulation modulates activity in interoceptive cortex, producing decreased right and increased left interoceptive cortex activity, and by consequence, an antidepressant effect (Conway et al., 2013; Kosel et al., 2011, Nahas et al., 2007). VNS-mediated decreases in right insula activity are particularly correlated with reduction of depression, supporting the notion that right insula regulates autonomic activity and subsequent negative affect (Conway et al., 2012). Similar studies likewise show that, in depressed patients, VNS modulates the default mode and functional connectivity of limbic regions, including the amygdala (Liu et al., 2016; Fang et al., 2016; Berthoud & Neuhuber, 2000). These findings further support the role of the vagus nerve in calibrating emotion and affect.

In summary, the vagus nerve regulates activity and representation in interoceptive cortex and the antidepressant effect of VNS supports this functional role of the vagus nerve. As previously discussed, exercise supports regulation of sympathetic responses as well as changes in vagal nerve traffic and improved interoceptive awareness (Mehling et al., 2018; Gibson, J., 2019). One possibility is that VNS derives its therapeutic influence by mimicking or enhancing the effect of exercise on sympathovagal and interoceptive function.

This possibility supports our hypothesis that the modern lifestyle results in interoceptive dysregulation. Interoception may be recalibrated through improved lifestyle choices; this improvement may be similarly facilitated by VNS.

Mindfulness and interoception

Mindfulness meditation is another treatment for depression growing in popularity. Like VNS, mindfulness may involve altering cortical representation of interoception. Mindfulness consists of attending to moment-to-moment internal and external perceptions in an observant, non-reactive way (Raffone & Srinivasan, 2010). Mindfulness meditation often involves attending to interoceptive sensations including breathing and heart rate. Some have proposed that improved interoception may be one underlying mechanism of mindfulness meditation (Gibson J., 2019).

Interoceptive training is a more refined technique that involves specifically attending to interoceptive sensations. This treatment has been shown to improve interoceptive accuracy and these changes correlate with reductions in anxiety (Sugawara et al., 2020). Neuroimaging studies have found that mindfulness training modulates activity in interoceptive cortex, particularly at the anterior insula (Farb et al., 2013). Furthermore, mindfulness improves interoception by increasing insula connection strength within the brain's overall connectome (Sharp et al., 2018).

In summary, one mechanism of mindfulness meditation involves therapeutic plasticity in interoceptive cortex, particularly in the insula. Functional changes to interoceptive cortex may reduce symptoms of interoceptive dysregulation and consequently result in improved mood. The relationship between mindfulness and interoception is explained by my hypothesis that the modern lifestyle is linked to depression. Lack of physical activity and reduced exposure to nature are features of modern life that result in deficits in interoceptive awareness and, consequentially, increased risk of depression. Indeed, research has shown that increased physical activity itself correlates with improved mindfulness and physiological awareness (Mehling et al., 2018). Thus, interoception is strengthened by increased attention to and involvement of bodily faculties, explaining one mechanism of mindfulness meditation.

Conclusion

I have shown that emotion evolved from homeostatic circuity and, consequently, that affective components of emotion are provided by cortical areas representing internal states. Depression is therefore a disease of interoception, characterized by persistent negative affect resulting from misinterpreted interoceptive sensations. One proximal cause of depression is therefore interoceptive dysregulation. I proposed that the evolutionary origin of depression is a lack of consistency between the modern lifestyle and the more naturalistic environment to which humans are adapted. Thus, deficits in light exposure and excessive sedentary activity are each strong risk factors for depression and interfere with mood by means of dysregulated interoception.

Interoception itself is represented and integrated in interoceptive cortex, particularly in the insula. Abnormalities in insular activity are closely associated with depression; In addition to exercise, vagal nerve stimulation modulates this insular activity to result in elevated mood. Similarly, mindfulness meditation may evoke therapeutic changes to interoceptive cortex. The efficacy of exercise, VNS, and mindfulness meditation as treatments for depression supports my hypothesis that depression results from incongruence between the modern lifestyle and our evolutionary legacy.

The understanding that depression originates from a mismatch between modern life and the conditions to which we are adapted is highly relevant in today's society. As we depart from our evolutionary past which involved constant physical activity and connection to nature, we can expect the incidence of depression to increase. This evolutionary paradigm may give rise to improved treatments of depression and mood disorders. Vagal nerve stimulation, exercise, and mindfulness meditation will prove increasingly useful as treatments for depression. Combining these treatments may help address refractory depression not treatable by pharmacological antidepressants.

Future Research

Research into the exact relationship between mindfulness training and interoceptive cortex would be beneficial; I suggest a neuroimaging study to test the correlation between changes in insular connectivity resulting from mindfulness training and improvements in depression severity. A correlation between mindfulness-induced neurological changes and improvement in depression would further establish the positive effect of mindfulness meditation on emotion. Similarly, neuroimaging studies should be conducted to assess interoceptive cortex reorganization in response to exercise or changes in light exposure. Studies should also be performed to determine which patients are most susceptible to treatments such as exercise, vagal nerve stimulation, or mindfulness meditation.

Recent scholarship has indicated the body's microbiome as affecting depression. Changes in microbiota composition have been reported to effect changes in mood via the "gut-brain axis". One possibility is that this gut-brain interaction is mediated by the vagus nerve, which innervates the viscera hosting gut flora. One intriguing approach for future research could involve measuring the effect of microbiota transplantation on sympathovagal balance.

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