University of Nevada, Reno

Psychoneuroimmunology: The Communicative Relationship Between the Environment, the Brain, and the Immune System

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by

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ABSTRACT

Depression is prevalent in the general population. Because of this, mental health has become a more important aspect of overall well-being. The focus on mental health has helped bridge gaps in medical practice. In terms of patient care, it is important to understand that the body is composed of multiple subsystems that are integrated into one large physiological system. The purpose of this thesis is to provide a thorough understanding of how strong the mind-body connection is, by taking into account both mental and physical health within the realm of psychoneuroimmunology (PNI). PNI is the scientific study that bridges psychology to the physiology of the nervous and immune systems. This thesis works to examine the following question: **To what extent does stress and depression affect the homeostatic functioning of the nervous and immune systems?** The findings suggest that there is a strong, intimate relationship between the mind and the body.

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LIST OF TERMS

Amygdala
Brain structure involved with emotion processing

Anhedonia
Difficulty with feeling pleasure

Anti-inflammatory
Substance used to reduce inflammation

Attenuation
Reduction of intensity

Bidirectional
Pathway that functions in two directions

Control
Variable kept constant for comparison during experimentation

Cortisol
Hormone released during a stress response

Cytokine
Chemical messengers of the immune system involved in intercellular signaling

Depression
Mood disorder characterized by a mental state of prolonged sadness

Downregulation
Process in which a cell decreases in quantity

Emotion
Intuitive mental state used as a means of motivation

Endocrine
Relating to hormone secretion by specific glands

Environment
External stimulus (or stimuli) that an organism interacts with

Glucocorticoid
Class of steroid hormones

Hippocampus
Brain structure involved with learning and memory

Homeostasis
Maintenance of physiological equilibrium

Hypothalamic-pituitary-adrenal (HPA) axis
The neuroendocrine stress system

Hypothalamus
Brain structure involved with maintaining homeostasis of the autonomic nervous system

Immunology
Biological study of the immune system

Knockout
Removal of specific variable; used to test effects during experimentation

Limbic system
Set of brain structures involved with emotion and motivation

Lymphocyte
White blood cells

Macrophage
Immune cell that engulfs foreign substances and debris

Modulation
Control over a specific process

Motivation
Reason for particular behavior

Negative feedback
Hindrance of a function or mechanism

Neurobiology
Biology of the nervous system

Neuroendocrine
Pertaining to both the nervous and endocrine systems

Neurogenesis
The brain's ability to both make modifications to already existing neuronal connections and also create new neuronal connections

Neuron
Fundamental cell of the nervous system; means of signal transmission

Neuropharmacology
Pertaining to the influence of drugs on the nervous system

Neuroplasticity
The brain's ability to alter its neuronal connections to deal with certain experiences

Neuroscience
Overall scientific study of the structure and function of the nervous system

Neuroticism
Negative emotional state characterized by mood swings

Pathophysiology
Abnormal physiology

Personality
Innate characteristics of an individual

Physiology
Study of the function of body functions

Proliferation
Quantitative increase

Pro-inflammatory
Substance used to increase inflammation

Psychology
The study of the human mind and behavior

Psychoneuroimmunology (PNI)
The scientific study that bridges psychology to the physiology of the nervous system and the immune system

Sickness behavior
Decreased behavior/arousal caused by injury or infection

Stimulus
Event that provokes a reaction

Stress
Stimulus that is difficult to emotionally cope with

Subsystem
One system within a larger system

T cell
Immune cell that functions as part of adaptive immunity

Upregulation
Process in which a cell increases in quantity

Vagus nerve
Cranial nerve involved with visceral organs

Valence
Positive or negative connotation of a subject

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CHAPTER 1: INTRODUCTION

1.1 The Mind-Body Connection

A typical emergency room visit involves a patient stating his or her chief complaint and symptoms, completing a physical examination, and receiving a diagnosis and treatment plan. In patients with chronic illness, physicians tend to focus on the physiological system that is of the patient's main concern. The old approach to medicine took into account only one system when physicians made a diagnosis. However, modern medicine has shifted views, focusing on the patient's entire body as one large, physiological system.

Aspects of mental health were thought to be constrained only to the mind, but scientific developments have begun to integrate psychological factors when physicians consider how they affect physical well-being (Ader, 1981). Emotions and thought processes not only help determine human behavior, but they also play crucial roles in modulating physiological functions beyond the mind. Research examined within this thesis shows an underlying relationship between negative psychological factors and physical signs or symptoms of health deterioration (Adler & Matthews, 1994). Psychoneuroimmunology (PNI) is the scientific study that bridges psychology to the physiology of the nervous system and the immune system. From a general standpoint, PNI analyzes the constant interactions going on between the environment, the brain, and the immune system – the triad of PNI – to provide a better understanding of how closely related mental health is to physical health (Ader, 1981; Ader, Felten, & Cohen, 1991). Advancing in the early 1980s, this scientific perspective on the mind-body connection is a young and developing field of medical research. Although a more novel type of

research, PNI is working to explain some of the causes behind physical illness by examining different aspects of the intimate mind-body relationship.

1.2 Objectives

The purpose of this research is to objectify the aversive effects of negative psychological factors on homeostatic physiological functioning, via effects on the nervous and immune systems. This thesis works to examine the following question: **To what extent does stress and depression affect the homeostatic functioning of the nervous and immune systems?** From a neurobiological standpoint, the research focuses on changes to certain aspects of the HPA axis, as well as the wiring and development of the nervous system, as a result of stressors and a negative psychological mindset. Though there are many aspects of the immune system involved in immune responses, this research will focus on the physiological roles of the T cell, one of the most important lymphocytes in modulating immunity. It is hypothesized that negative psychological factors play a significantly detrimental role in altering both neurobiological and immunological responses, by examining the physiological changes associated with depressive mental conditions. Before dissecting the interactions that occur within this complex system, it is important to establish the fundamentals of the three disciplines and how they are involved in PNI.

1.3 Psychology

Humans are complex organisms that constantly interact with their environment. They process their surroundings through their own perspectives, and react based on their personalities and how they are able to cope with certain situations. Most of these experiences are affected by emotions, in the sense that responses to given circumstances

occur in an instinctive manner. Before delving into the processes behind the physiological psychology of emotions, it is important to establish the rudimentary aspects of emotions and how they come about. Viewing the brain from an anatomical perspective, the limbic system is involved in several higher functions of the brain, including emotional processing. However, there is one structure in particular that deals with emotional functioning – the amygdala. In 1956, British psychologist Lawrence Weiskrantz conducted studies which suggested that lesions to the amygdala alone caused inhibition towards connecting external stimuli to any means of motivation (Lewis, Haviland-Jones, & Barrett, 2008). Monkeys that suffered damage to the amygdala were unable to emotionally realize the significance of any stimuli, especially if they were negative. In other words, subjects were unable to connect threatening stimuli to fear, and thus did not elicit any reaction even when they were confronted with danger. This disconnection due to an absence of the functionality of the amygdala highlights its importance in regulating emotional response.

After establishing where emotions arise, it is important to understand how emotions are integrated into an individual's life. There are some accounts that explain how emotions are a temperament – that is, they are an innate aspect of personality. Children who develop well in self-regulation are less likely to display a sense of neurosis, or mental instability, when faced with aversive stimuli. Some children, however, develop poorly in self-regulation, and as a result they react in disruptive and hindering ways when dealing with unpleasant stimuli (Lewis et al., 2008). Self-regulation is essential in controlling emotions, as this regulation keeps emotions from becoming extreme for an individual and his or her surroundings. When an individual suffers from some form of

fear, stress or anxiety (e.g., posttraumatic stress disorder or social anxiety disorder), this can interrupt the cognitive ability to regulate emotions, allowing them to have adverse effects on the mind as well as the body (Kim et al., 2011). As a result, it is critical to examine how emotions extend beyond the mind to reach and affect the nervous and immune systems.

1.4 Neuroscience

The brain is a highly complex organ that controls all sensation, processing, and responses that occur between the environment, the mind, and the body. While signals are constantly sent throughout the nervous system, certain structures are involved in stress response. The neuroscience of mental disorders greatly focuses on the abnormal functioning of the hypothalamic-pituitary-adrenal (HPA) axis. When a stress response is triggered, the hypothalamus secretes two hormones – corticotrophin-releasing factor (CRF) and vasopressin (AVP). This secretion activates the pituitary gland, which then secretes adrenocorticotrophic hormone (ACTH). The final step of the stress response occurs when ACTH stimulates glucocorticoid secretion from the adrenal cortex of the adrenal gland. In humans, the glucocorticoid – or "stress hormone" – is known as cortisol, and this plays an important homeostatic role by regulating different mechanisms inside the body (Pariante & Lapiz-Bluhm, 2014).

In addition to breaking down the different neural structures involved in stress response, it is important to note that the brain is always wiring – and rewiring – to adapt and develop to different situations. In relation to stress, humans can be confronted with an aversive situation that requires an individual to adapt to the environment in order to overcome such adversity. Along with this adaptation in human behavior, the brain

undergoes actual neurobiological changes that correspond to behavioral changes. Otherwise known as neuroplasticity, the brain is capable of altering its neuronal connections to deal with certain experiences. One form of neuroplasticity that aids an individual with learning and adapting, especially to difficult situations, is the brain's ability to both make modifications to already existing neuronal connections and also create new neuronal connections – neurogenesis (Pariante & Lapiz-Bluhm, 2014). Due to the constant changes in brain structure and wiring based on given experiences, it is possible to see just how complex and dynamic the nervous system is. The nervous system is always adapting in response to changes happening both inside and outside of the body, supporting the notion that the mind-body connection is one large physiological system. In addition to neurobiological adaptations to stress, examination in immunology provides further evidence that mental adversity can have physiological consequences to an organism's homeostatic functioning.

1.5 Immunology

In general, the purpose of the immune system is to defend the body and fight against pathogenic organisms (viruses, bacteria, parasites and fungi) that enter the body and threaten its health. Leukocytes, commonly known as white blood cells, are a prominent aspect of the immune system. More specifically, lymphocytes – which are comprised of natural killer (NK) cells, B cells and T cells – make up about 20% of leukocytes, and are intended to be a means of specific defense. NK cells attack cells that are virally infected. B cells are important for producing and secreting antibodies that recognize and bind to specific strains of antigens. T cells are involved in cell-mediated immunity: cytotoxic T cells directly search and destroy target cells, helper T cells

augment immune responses, and suppressor T cells diminish the responses (O'Leary, 1990).

Cytokines provide a means of intercellular signaling amongst the cells of the immune system. These polypeptide hormones work as mediators that activate and send signals intercellularly in order to regulate immune responses. Cytokines are produced by a variety of immune cells, mainly the activated macrophage, and interact within the immune system in different ways – autocrine, paracrine, and endocrine responses. In other words, cytokines can interact on the same cell that secretes them, on adjacent cells, and even on distant cells, respectively (Zhang & An, 2007). Cytokines are subcategorized into two types, pro-inflammatory and anti-inflammatory, and play a vital role in immunity by mediating cell response in two different ways (Kiecolt-Glaser, McGuire, Robles, & Glaser, 2002). It is well documented that negative emotions can interfere with the homeostatic functioning of these immune cells and proteins.

1.6 Methodology

The main approach to this scientific research is to focus on textual research and previous experiments that examine different aspects of PNI. This research is literature-based, so the information is drawn from existing literature on the topic. While experimentation could have been conducted to investigate specific aspects of PNI, a literature review is more advantageous to this research. A literature review gives the opportunity to examine different areas of this discipline, as opposed to researching and testing a more specific hypothesis. This research involves an examination of various scientific articles, dating from the start of PNI research to more recent studies within the past five years. The databases used in this research were Web of Science, PubMed, and

the Mathewson-IGT Knowledge Center website. Filters in the search engines included having peer-reviewed articles, and a majority of the articles reviewed were published within the last ten years. Key words used to search articles included, but were not limited to: psychoneuroimmunology, psychology, neuroscience, immunology, stress, depression and emotion. The current research focuses to integrate data and findings of previous studies; however, this thesis will integrate them within a new perspective and approach to looking at PNI in order to create a more general understanding for both a medical and personal health application.

1.7 Significance

This research aims to analyze the mind-body connection within the context of how negative psychological factors affect the functioning of the nervous system and immune system. The current research will consider the different subsystems and interconnecting pathways of the body to ultimately show how all aspects of physiology are connected and integrated into one large system. Specifically, this paper investigates how stress makes alterations to the nervous system, further changing the homeostatic functions of the immune system to ultimately generate a depressive behavioral response. Negative psychological factors play a significant and detrimental role in altering immunological responses, by ultimately upregulating cytokine activity and increasing pro-inflammatory response, thus triggering greater susceptibility to illness. T cells and their corresponding regulation of the production of cytokines, the chemical messengers that are important to intercellular signaling and modulating the inflammatory response (Furtado & Katzman, 2015; Tausk, Elenkov, & Moynihan, 2008), are key components to the pathophysiology of the overall system. This paper reviews various sources of

literature and compiles data to support the notion that psychological stressors can interfere with homeostatic mechanisms. Expected results supplement existing research by examining crucial aspects of neuroscience and immunology, to further understand the relationship between the environment, the nervous system, and the immune system.

The data and findings presented in this thesis may help educate patients, physicians, and anyone interested or involved in the care of patients who suffer from stress-related disorders. Because chronic illness and depression are prevalent in the general population, it is important to understand that mental well-being is just as important as physical well-being, and how the two function together within a single body. Emphasizing the importance of psychology in healing patients will optimize patient care as a whole, bringing greater satisfaction and more productive healing to patients.

CHAPTER 2: EXPORATION OF THE SUBSYSTEMS

After establishing the fundamentals of the three disciplines involved in PNI, it is important to further dissect the subsystems involved in each discipline. While psychology, neuroscience, and immunology are three subsystems with their own functions, there are certain structures that exist and processes that occur to allow each subsystem to integrate and respond to stress and depression. An examination of these subsystems provides a better understanding of what goes on both inside and outside of the mind and body.

2.1 The Limbic System

2.1.1 Amygdala, Hippocampus and Hypothalamus

Neuroscientists studying the limbic system in the late 19th and early 20th centuries, including Pierre Paul Broca as well as Klüver and Bucy, primarily defined the limbic

system as an area of the brain that serves the purpose of integrating and processing information involved in both emotion and motivation (Morgane, Galler, & Mokler, 2005). While there are various anatomical structures involved in this system, a few specific structures are particularly relevant to PNI:

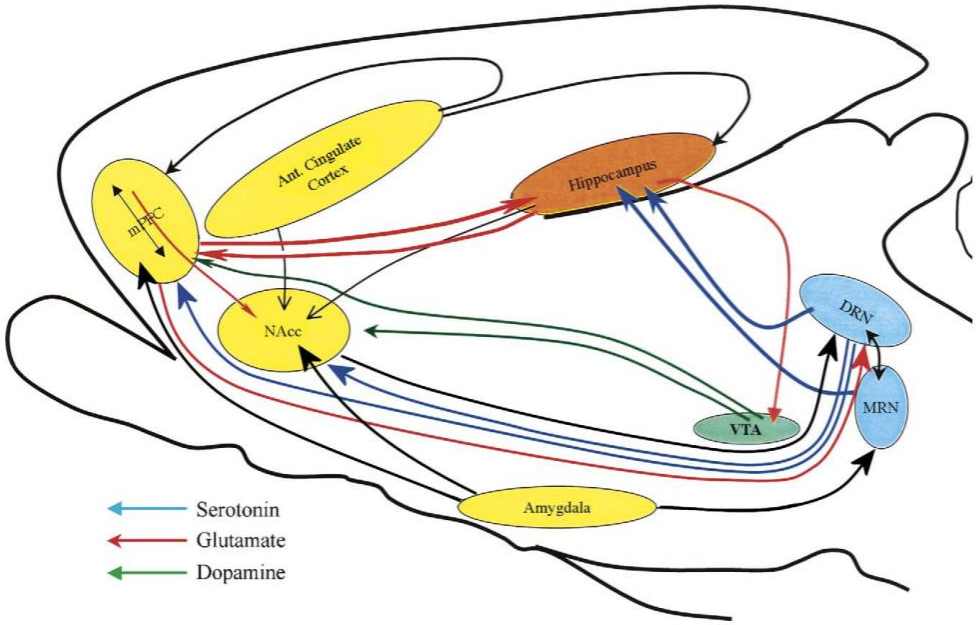

Figure 1. Limbic system network (Morgane et al., 2005).

Figure 1 illustrates the general mapping of the limbic system, including major structures as well as their respective neuronal connections. The structures relevant to PNI are the amygdala, the hippocampus, and the hypothalamus (not illustrated in figure).

The first structure to note is the amygdala. This structure facilitates the processing of emotion, and also mediates stress effects on the hippocampus through its neural projections to the hippocampal formation. In addition, the amygdala shares an important relationship with the hypothalamus. The amygdala plays a key role by moderating the endocrine aspects of hypothalamic functioning. This amygdalo-hypothalamic projection

suggests the importance of the limbic system in integrating stressful stimuli, and sending this processed information to the rest of the nervous system (Morgane et al., 2005).

In terms of learning and memory, the hippocampus is the structure responsible for associative learning, as well as memory formation and consolidation. When an individual experiences a stressful or traumatizing event, neural projections from the amygdala are sent to the hippocampus, and memory formation occurs to help the individual associate the experienced feelings and emotions with the stressful stimulus (Morgane et al., 2005). As a result, an organism's physiological response to stress can be triggered when a traumatic memory is recalled.

The final structure to note is the hypothalamus. Hypothalamic neurons project out of the limbic system and integrate themselves into the prefrontal cortex, where higher-level information processing and executive decision-making occur. Neurons also project from the prefrontal cortex into the hypothalamus, emphasizing the importance of this connection between the limbic system and the central nervous system (CNS) (Morgane et al., 2005). This physical connection between the environment and the nervous system, through limbic structures, creates the bridge that allows sensation from an environmental stimulus to be processed and become a motor response – the organism's ultimate behavior towards the environment or situation. Examination of the limbic system and its relevant anatomical structures provide an understanding of how the environment can influence mood regulation through integration and emotion processing of negative environmental stimuli. The mind processes this information in order to generate the body's physical response to the environment. The physical structures of the limbic

system allow for emotion processing, however the extent of and vulnerability to experienced emotions depend on the individual's personality and ability to manage stress.

2.1.2 Personality, Emotion and Depression

Personality – innate characteristics of an individual – is an important factor to consider with respect to emotion processing, because different personalities can create different predispositions when it comes to coping with stress. One highly studied personality trait associated with emotional arousal is neuroticism, a negative emotional state associated with mood swings (Kehoe, Toomey, Balsters, & Bokde, 2012). The researchers focused on neuroticism because it is a clinical risk factor for people who could develop anxiety and/or depression. High levels of neuroticism correspond with greater activation of the limbic system, further predisposing an individual to react with much more intensity to an emotionally arousing stimulus. According to Eysenck's biological theory of personality, increased neuroticism is also associated with decreased reward processing (Kehoe et al., 2012).

Kehoe et al. (2012) conducted a neuroimaging study to illustrate the effects of personality type on the neural links involved in emotion processing. Participants consisted of 23 right-handed, young, healthy women (mean age = 23.04 ± 3.46 years). Only women participated due to differences in emotional reactivity between genders. The stimuli were 190 colored photos of varying arousal levels, and were characterized as having either a positive or neutral valence (i.e., a positive or neutral connotation, respectively). The researchers used functional magnetic resonance imaging (fMRI) and examined blood oxygenation level dependent (BOLD) signals – contrast imaging – to see

if different levels of neuroticism affected the way participants rated certain images based on arousal and valence (Kehoe et al., 2012):

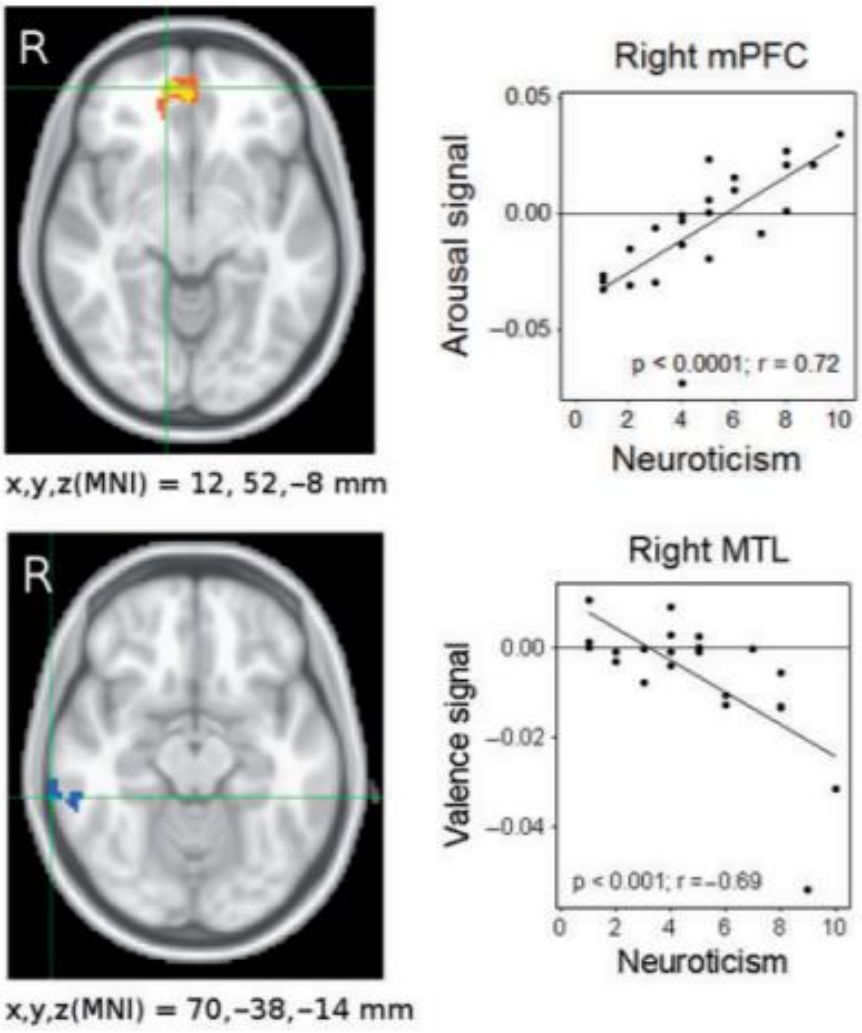

Figure 2. BOLD response in neuroticism (Kehoe et al., 2012).

The top half of the figure illustrates the measure of arousal, while the bottom half illustrates valence. The left demonstrates activated areas of the brain via fMRI scans, and the right shows measured response based on how individuals reacted to different photos. The results of the study showed that neuroticism was positively correlated with arousal

intensity, and negatively correlated with valence intensity (Fig. 2). In other words, individuals who were considered highly neurotic had an increased response to a stronger arousal stimulus, but had a decreased response to a positive valence. This finding is consistent with the idea that depressive patients can be aroused with greater intensity of a stimulus, but can also have more difficulty responding to a positive stimulus. The findings of this study relate to the idea that a certain personality can make someone more susceptible to developing symptoms of depression, and further make that individual more vulnerable towards intense or negative stimuli. It is possible to speculate how mood disorders can greatly alter emotion processing to change the way an individual interacts with his or her environment.

Without the limbic system, it would be difficult to associate emotions to different situations. As a result, a lack of motivation would prevent an individual from adapting to his or her environment, decreasing chances of survival. The limbic system is crucial in terms of allowing an individual to create meaning within his or her life. Emotion processing is necessary in order to learn, adapt, and feel a sense of purpose or meaning. After information is taken from the external world and processed within the psychological mind, the information is passed on to the body, where a physiological response can occur. The primary means by which environmental stimuli is integrated into the body is through the nervous system, where such stimuli are sensed and a response is created.

2.2 The Nervous System

2.2.1 HPA Axis in Depression

The hypothalamic-pituitary-adrenal (HPA) axis has been widely studied in terms of its relation to stress and depression, and research has noted neurobiological changes within patients suffering from increased levels of stress and/or major depressive disorder. When activation and functioning of the HPA axis become abnormal, negative feedback loops are impaired. This causes cortisol levels to increase in blood circulation, also known as hypercortisolemia, which is prevalent in depression. This feedback regulation is mediated by two intracellular corticosteroid receptors: mineralocorticoid receptors (MR) and glucocorticoid receptors (GR). The MR is found mostly in the hippocampus, and is found at a much lower concentration than the GR. The GR, on the other hand, is more distributed across the brain and is found at high densities in the hippocampus, amygdala, hypothalamus, and even the brain stem (Juruena, 2014):

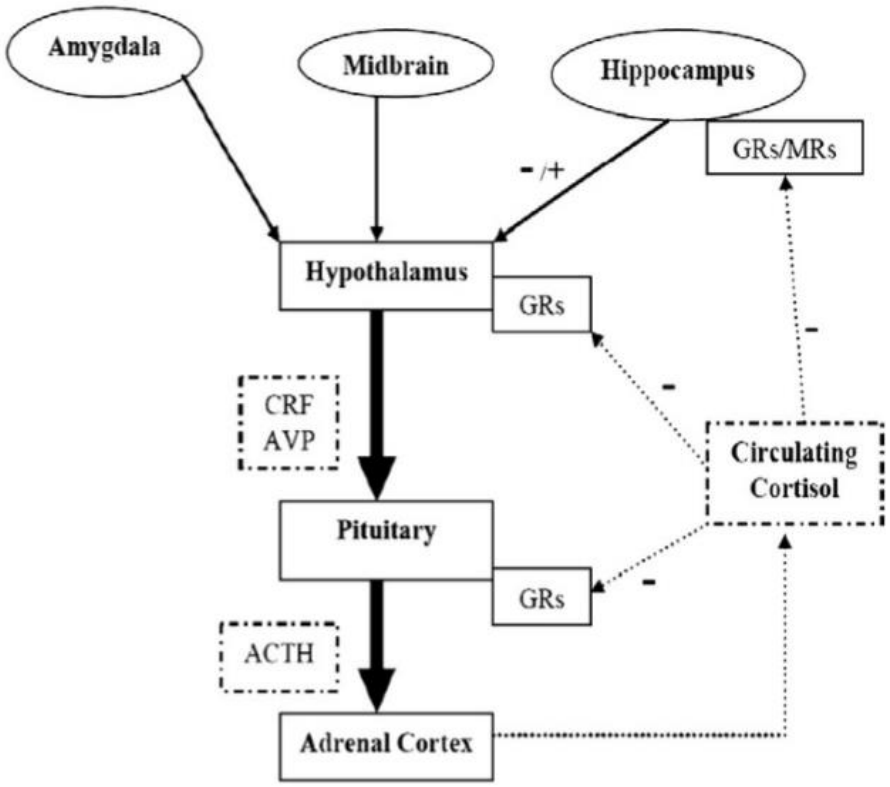

Figure 3. The hypothalamic-pituitary-adrenal (HPA) axis and its feedback mechanisms (Juruena, 2014).

Speculations on GR activity suggest that this receptor type is more involved in feedback mediation of depressed patients. As illustrated in Figure 3, there are GR receptors found at various locations of the HPA axis, demonstrating how active they are within the axis (Fig. 3). The high level of GR receptors suggests that they play a vital role in regulation of this negative feedback loop. While the MR mediates negative feedback under baseline cortisol conditions, the GR mediates such feedback when an individual undergoes stress and expresses high levels of cortisol concentration in the blood (Juruena, 2014).

Solomon et al. (2012) focused on the role of the GR in stress response and depression-like behavior to emphasize its importance in HPA axis regulation. The researchers used two groups – control and knock out – of both male and female mice to test the effects of GR absence within the brain. In order to test the differences in depression-like behavior, the researchers conducted a forced swim test (FST) and also tested sucrose preference on the mice (Solomon et al., 2012):

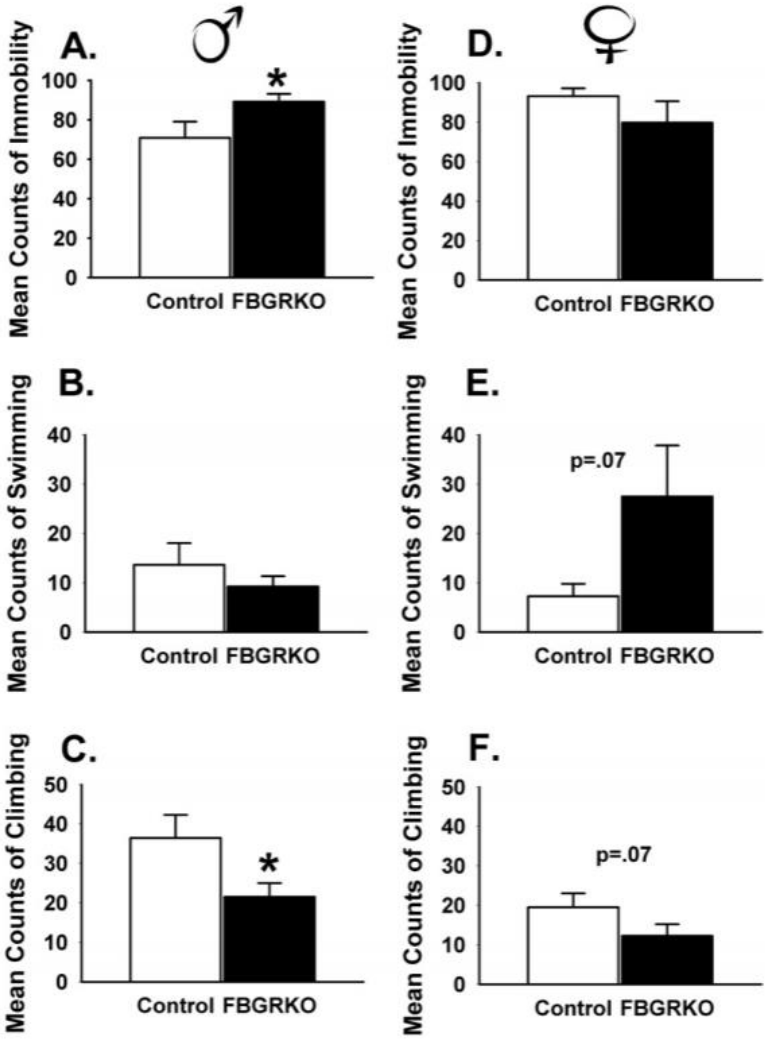

Figure 4. Forced swim test (FST) in control and forebrain glucocorticoid receptor knockout (FBGRKO) mice (Solomon et al., 2012).

Depression in the mice was measured in terms of sickness behavior. In the FST, the researchers measured movement of the mice in terms of immobility (Figs. 4A and D), swimming (Figs. 4B and E) and climbing (Figs. C and F). Female forebrain glucocorticoid receptor knockout (FBGRKO) mice displayed results that differed from the male FBGRKO mice. The female FBGRKO mice moved more than their control counterparts, and also exhibited increased swimming activity. However, the male FBGRKO mice demonstrated more depression-like and helplessness behavior: male FBGRKO mice moved much less than their control counterparts, especially with climbing (Fig. 4). While the female results differed from male results, suggesting an effect of biological sex on the functioning of the HPA axis, the male results were consistent with cortisol levels in the brain and depression-like behavior. When receptors were not present to bind glucocorticoids, the negative feedback loop was attenuated and HPA axis activity no longer functioned under homeostatic conditions (Solomon et al., 2012). The sucrose consumption test produced similar results:

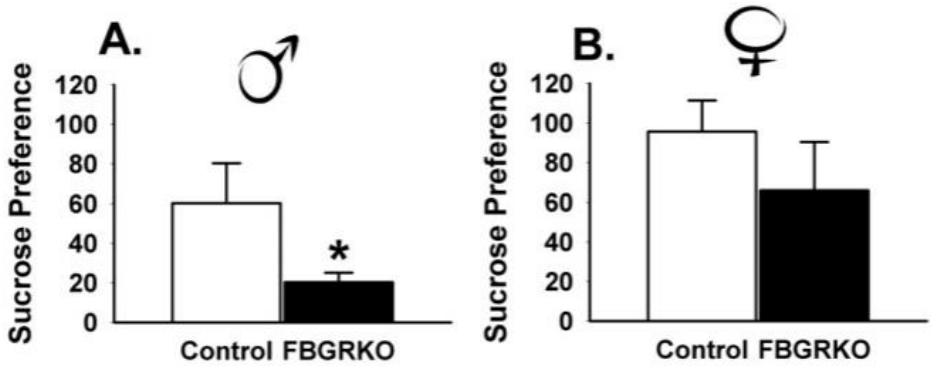

Figure 5. Sucrose consumption in control and forebrain glucocorticoid receptor knockout (FBGRKO) mice (Solomon et al., 2012).

In both cases, the FBGRKO mice consumed less sucrose than the control mice (Fig. 5). This finding is consistent with anhedonia, or difficulty with feeling pleasure, in depression patients (Solomon et al., 2012). Even when a depressed subject is presented with a positive stimulus, the subject does not find any purpose to engage with the stimulus. The findings in this study highlight the importance of the HPA axis in regulation of depression-like behavior, by demonstrating the relation between decreased motivation and pathophysiology of the HPA axis. Even though glucocorticoid receptors are a small aspect of the HPA axis, their role in negative feedback suggests that they are vital in the regulation of neuroendocrine mechanisms and expression of depression symptoms. This relationship between depression and neurobiological changes to the HPA axis demonstrates the connection going on between the mind and the body.

2.2.2 Hippocampal Neurogenesis

Studies in animal models of depression have shown that a decrease in hippocampal neurogenesis can negatively impact the functioning of the HPA axis. Researchers have focused on the relationship between neurogenesis in the hippocampus and how this neurobiological process affects regulation of the HPA axis (Mahar, Bambico, Mechawar, & Nobrega, 2014). Figure 6 illustrates the processes involved in stress response:

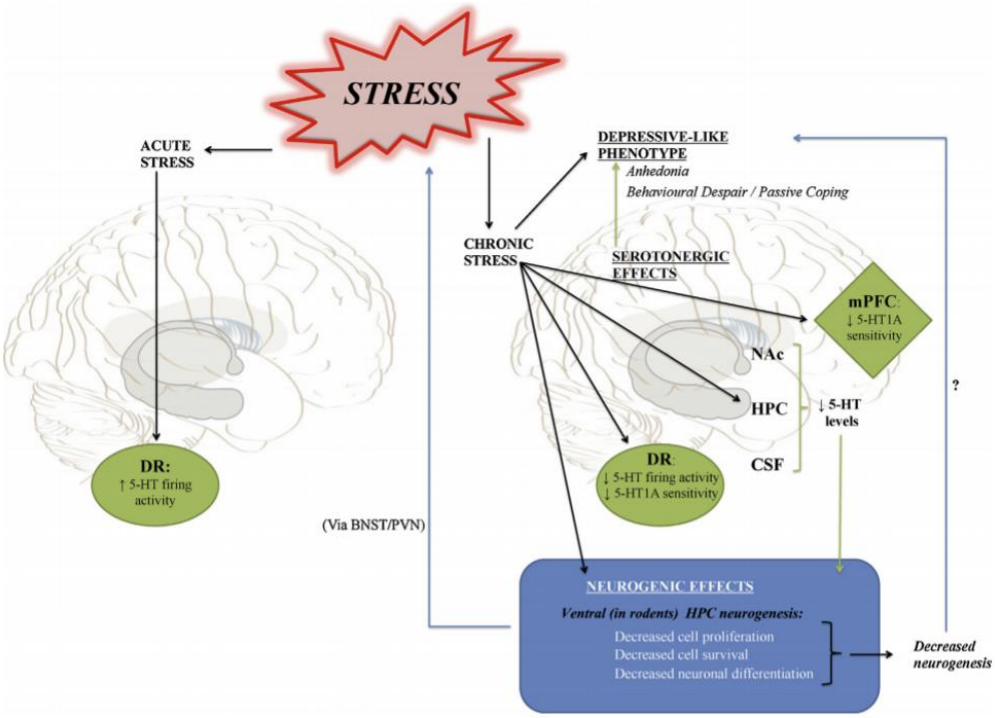

Figure 6. Effects of stress on hippocampal neurogenesis (Mahar et al., 2014).

While acute stress triggers a quick, direct stress response in the form of an increase in serotonergic (5-HT) firing, the stress response due to chronic stress is much more complex. Although chronic stress itself directly leads to depression-like behavior, this stress also indirectly reinforces this behavior through alterations in neurogenesis. Attenuation of cell proliferation, cell survival, and neuronal differentiation (Fig. 6) slows down the growth and development of neurons in the brain. Without these fundamental building blocks – in the case of the brain, neurons – it is difficult to create connections within the brain, which further makes it difficult for an organism to wire its brain for adaptation to given circumstances. In terms of coping with stress and depression, an organism loses this neuroplasticity that can be used to maintain homeostatic functioning of the brain.

As shown in the research, the brain is a sophisticated organ that constantly works to develop itself and enhance its functioning. Stress, threats, and dangerous stimuli are all processed as sensory information, and structures within the brain work to use this information as a means of learning and adapting. These neurobiological adaptations serve to allow an organism to be better equipped for any potential threats that may exist in his or her environment. Similar to the nervous system, the immune system also adapts to illness and injury caused by the environment. Immunological adaptations occur to protect the individual from further harm.

2.3 The Immune System

2.3.1 The Macrophage

The macrophage – one of the most important lymphocytes in the immune system – could arguably be the most quintessential cell in physiology, due to its ability to perform in various aspects of biological development and maintenance. This cell type is the most diverse hematopoietic stem cell, as it is able to differentiate into various blood cells and tissues throughout the body. With its flexibility in differentiation, it is possible to see just how crucial the macrophage piece fits into the puzzle of physiology. Extensive research emphasizes the immunological work of the macrophage, however this cell also works heavily to assure proper assistance with development of different cell types in order to achieve optimal conditions for organ growth and homeostasis (Wynn, Chawla, & Pollard, 2013):

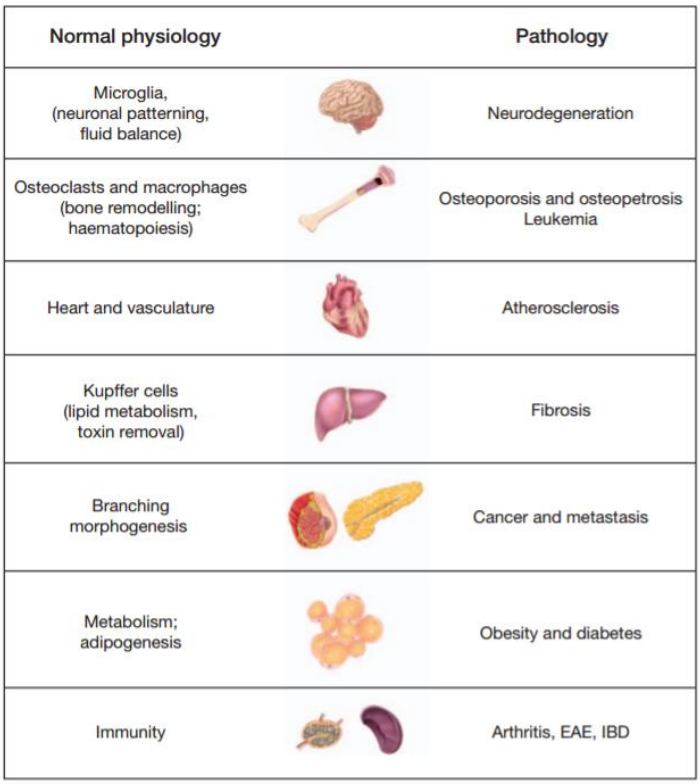

Figure 7. The several roles of the macrophage in physiology (Wynn et al., 2013).

As illustrated in Figure 7, the macrophage is used in many different areas of the body. The left column describes the various roles in maintaining normal physiology, the middle column illustrates the organs involved, and the right column describes potential illnesses that could occur if the macrophage is not present to develop homeostatic physiology (Fig. 7). Once cell tissue differentiation is established, the macrophage further works to maintain homeostasis of cells. One of the most important functions of the macrophage is its role in inflammatory disease response. Essentially, the macrophage produces and secretes cytokines that signal messages to other immune cells in order to recruit lymphocytes to the target site in the body (Wynn et al., 2013). Through this chemical messaging, the macrophage is able to distribute its instructions all over the body, giving

the body an advantage towards adaptation and survival. Most homeostatic processes, such as those listed in Figure 7, would be difficult to achieve without this communicative mediator working to connect all the subsystems together into one large physiological system.

2.3.2 T Cells

Another crucial aspect of the immune system is the T cell. While the macrophage is an important cell in innate immune response, the T cell plays an important role in adaptive immune response. Studies have shown a relationship between the pathophysiology of depression and the involvement of the T cell in these processes, through the T cell and its roles in neuroprotection and anti-inflammatory response (Miller, 2010):

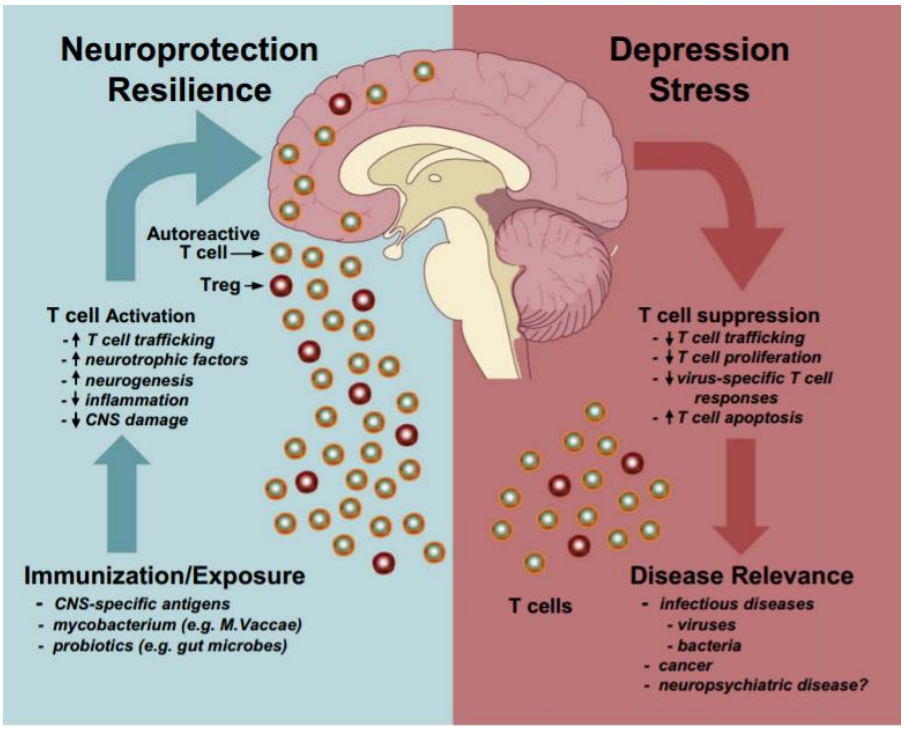

Figure 8. Autoreactive and regulatory T cells (Miller, 2010).

Figure 8 provides a layout for how an increase in T cell production helps reduce physiological damage caused by stress and depression, while a decrease allows for the persistence of disease. The cell responsible for the neuroprotective response is the autoreactive T cell. Evidence was shown through labeling these T cells in a subject that suffered from injury to the CNS. Once the subject was treated with an immunization injection that contained these T cells, the T cells traveled directly to the injury location to help reduce CNS damage (Miller, 2010). The regulatory T cell is the T cell responsible for inflammatory response. As the name implies, these cells work to regulate the extent of an immune response and ensure that only an appropriate amount of immune response occurs. In other words, chronic inflammation is downregulated in order to keep an individual within homeostatic conditions. Without this type of T cell, immune response would occur in excess and cause further damage to the body instead of healing (Miller, 2010). These examples of T cell function demonstrate the delicacy of the immune system, as well as how extensive the immune system functions to affect different areas of the body. With respect to PNI, changes to one subsystem can cause changes to another subsystem, illustrating the intimate connections going on throughout the body.

While some T cells help prevent damage from stress and depression, other T cells can have opposing effects on the body. Beurel, Harrington and Jope (2013) looked at the association between high levels of T helper 17 (Th17) cell concentration and expressed depressive behavior in male mice. Th17 cells are differentiated forms of $CD4^+$ T cells, which are known to be a large aspect of adaptive immunity (Beurel, Harrington, & Jope, 2013). Previous literature supports the notion that Th17 cells may promote depression-like symptoms, due to the fact that their presence coexists with signs of damage to the

CNS. The researchers created three conditions to test the effects of Th17 cells on depression: administration of Th17 cells, $CD4^+$ T cells, or phosphate buffered saline (PBS). Th17 was used to test the hypothesis, while $CD4^+$ and PBS were used as controls. $CD4^+$ was tested to see if the undifferentiated form of this T cell would have any similar effects on depressive behavior as Th17. PBS, which was used as a vehicle to administer the injections, was tested to see if just the injection pain could have induced depression behavior during the trials. During one of the tests, the researchers examined all three mice conditions and their responses to low-intensity inescapable footshocks (IES) (Beurel et al., 2013):

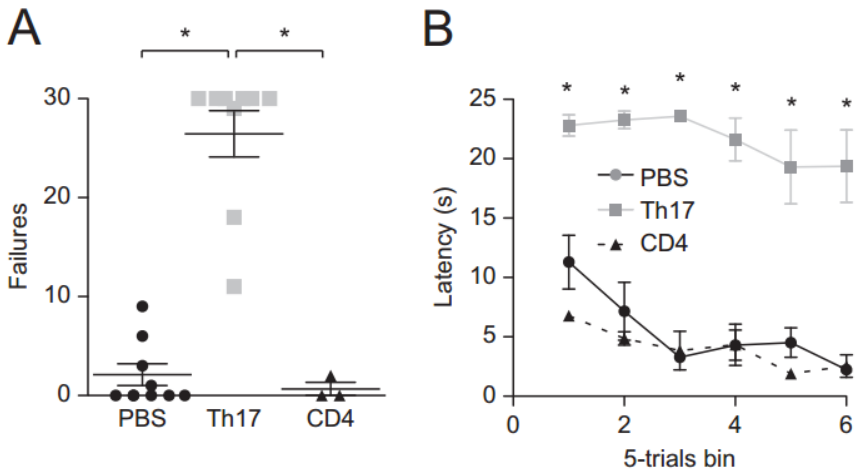

Figure 9. (A) Escape failures after low-intensity IES, and (B) average escape latency in PBS, Th17 and $CD4^+$ mice (Beurel et al., 2013).

The researchers tested locomotor activity in all three conditions to see which mice displayed depression-like behavior under stressful situations. While the shock was tolerable to both $CD4^+$ and PBS mice, and both conditions did not exhibit learned helplessness behavior, the Th17 mice displayed high levels of helplessness behavior (Fig.

9). Figure 9A shows how when compared to the control mice, the Th17 mice had a high escape failure rate. In addition, the average escape latency in Th17 was also high in comparison to the controls (Fig. 9B). The lack in attempts to evade the shocks, and also the delayed responses to try to escape, both provide evidence that the Th17 mice had a decrease in motivation. This lack of motivation is strongly associated with depressive behavior. This connection between levels of Th17 in the body and depression-like behavior suggests that negative psychological factors can lead to alterations in inflammatory response that can harm an individual. Even though some T cell subtypes are produced for the purpose of reducing inflammation, other subtypes can work against the body to damage its physiology, especially if these subtypes proliferate under pathophysiological conditions. The notion that various aspects of the immune system can either help or hurt the body supports the fact that the immune system is delicate. As illustrated with the T cell, this lymphocyte can differentiate into specific kinds of T cells, producing different functions and responses. There are several moving parts to the immune system, which creates more potential for pathophysiology to occur. Thus, it is important to study how the immune system is mediated by and interconnected with other subsystems of the body.

2.3.3 Cytokines

Within the realm of PNI, studies show how cytokines are involved in the etiology of depressive disorders. Different cytokines involved include, but are not limited to, interleukin-1 (IL-1), IL-6, tumor necrosis factor α (TNF-α), and interferon γ (IFN-γ) (Connor & Leonard, 1998; Dantzer, 2001; Maes et al., 1997; Maes et al., 1995; Schiepers, Wichers, & Maes, 2005). Essentially, there is increased activity of cytokines

in people who express symptoms of depression, due to the inflammatory response. This hyperactivity can create changes in the nervous system, which leads to potentially being more susceptible to depression.

CHAPTER 3: INTERCONNECTING PATHWAYS

While it is interesting to note the several moving parts of each subsystem, it is more interesting to see how all these moving parts coordinate with one another and work together to create the one, large physiological system. PNI demonstrates these interconnecting pathways, showing how environmental stimuli are processed within the brain, how this processed information alters immune response, and how these alterations can cause further changes to an organism's ultimate behavior towards their environment.

3.1 Environment to the Brain

There are many stressors in the environment that pose as hazards to mental and emotional well-being. Humans are social creatures, which suggests that the social aspect of life could potentially create an aversive environment for an individual. Lieberwirth, Liu, Jia and Wang (2012) conducted a study to examine the effects of social isolation on neuronal development. The researchers used the prairie vole, a highly social animal, as the experimental model. In one of the experiments, the researchers injected the prairie voles with the cell division marker 5-bromo-2'-deoxyuridine (BrdU) in order to label the neurons and visualize effects of isolation on cell proliferation and survival in both the amygdala and the hippocampus (Lieberwirth, Liu, Jia, & Wang, 2012):

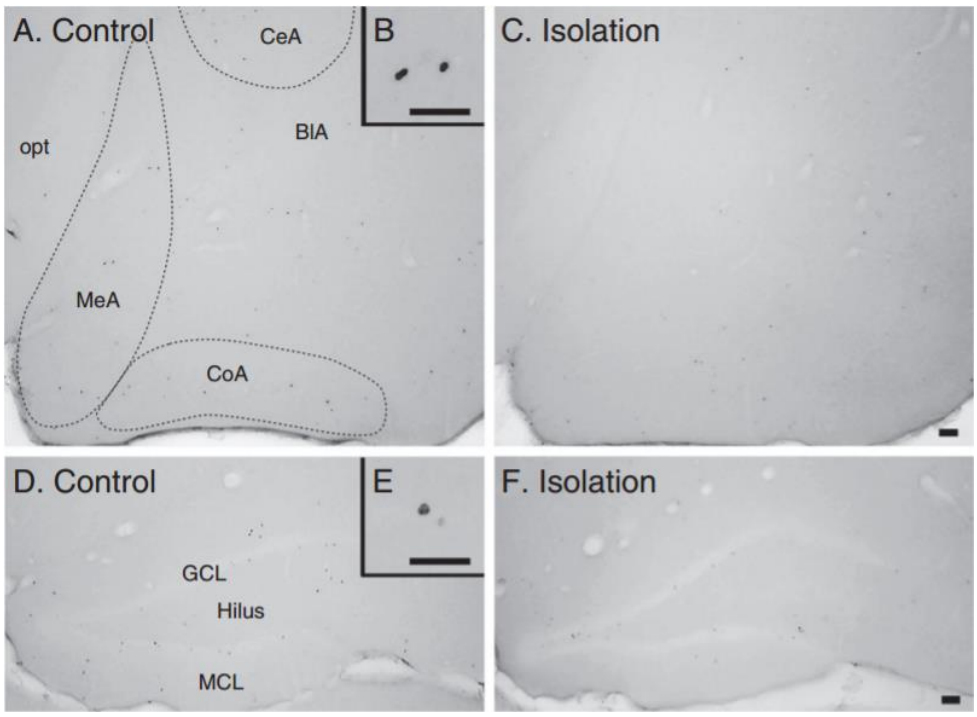

Figure 10. Cell labeling in brain sections showing the amygdala (A – C) and the hippocampus (D – F) (Lieberwirth et al., 2012).

Subjects were randomly assigned to one of two conditions: pair-housed (control) and single-housed (isolation). The results revealed that subjects treated with the isolation condition were subjected to a large decrease in cell survival (Fig. 10). When compared to the controls, the brain sections of the isolated prairie voles showed less cell proliferation, suggesting that isolation could have affected neurogenesis in both the amygdala and hippocampus. This finding proposes the idea that even though mental adversity is not easily objectified on an external level, these hardships can still have consequences on the homeostatic conditions of the brain. Disruption of homeostasis due to stress and depression is correlated with actual physiological changes to the brain. Once changes are made in the brain, the body responds by creating changes to immune response.

3.2 Brain to the Immune System

3.2.1 Vagus Nerve Circuit

The main purpose behind the CNS is that the brain and spinal cord work together to process external sensory information, and send motor responses to the rest of the body. Sensation and response are achieved through afferent and efferent neurons, respectively. One of the main responsibilities of the nervous system is to sense threats and trigger an appropriate response to keep the individual safe from harm. This responsibility includes sensing inflammation and being able to modulate certain mechanisms to regulate that inflammatory threat – the inflammatory response (Olofsson, Rosas-Ballina, Levine, & Tracey, 2012):

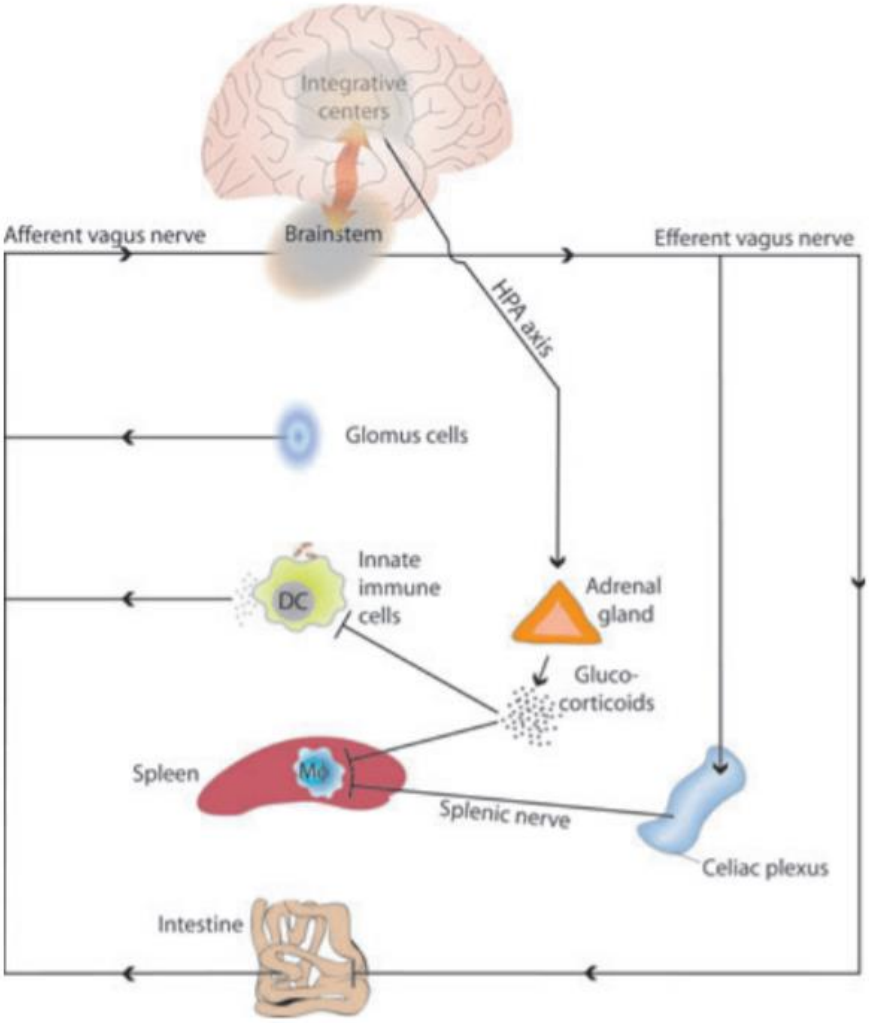

Figure 11. The inflammatory reflex (Olofsson et al., 2012).

As Figure 11 illustrates, when an infection or injury is introduced to an organism, cytokines are activated and send signals via afferent neurons in order to reach the brain. Sensory input is sent up the vagus nerve and into the brain, where information is processed and an appropriate motor response can be generated. As a result of the infection or injury, efferent neurons send signals to organs in the body that are responsible for initiating an immune response. In this case, signals are sent to the spleen.

These efferent neurons encourage the release of acetylcholine – a neurotransmitter – from $CD4^+$ T cells, which communicate the signal to immune cells to then stop the production of cytokines and terminate the inflammatory response (Olofsson et al., 2012; Rosas-Ballina et al., 2011). While cytokines first act as a response messenger, to relay the signal that injury has occurred to the body, they are then shut down as a result of signals from the brain once an inflammatory response has been triggered. This vagus nerve circuit works to ensure that only an appropriate immune response occurs, without further damaging the body.

This communication between the immune system and the nervous system demonstrates the complexity of the physiological functions of the body as a whole. All parts of the mind and the body flow through these interconnective pathways, and every subsystem of the body works together in a harmonious manner to ensure that homeostasis is achieved in the organism. Ideally, homeostasis is maintained, however when there is a disruption in homeostatic functioning of the physiological system, this causes further alterations to the system. As a result, organs develop to have a pathophysiological function, causing harm to the organism. When the immune system undergoes pathophysiological changes, this response is sent back up to the brain, where more changes occur.

3.3 Immune System to the Brain

One way to look at the immune system and its relation to mood disorders is to examine the inflammatory biomarkers involved in depression. As it is known, major depression is characterized by different kinds of sickness behaviors, including difficulty with concentration, weakness, decreased energy levels, and decreased appetite (Muller,

Myint, & Schwarz, 2011). From a psychopathological standpoint, it is possible to see how inflammation is mediated by different pro-inflammatory cytokines, based on the level of depression being experienced at the time. One direct link between the immune system and the brain is through afferent neurons. These neurons actively target the amygdala, which is responsible for emotion response and regulation. Cytokines diffuse through the choroid plexus – an area of the brain that generates cerebrospinal fluid in the ventricles – and also circumventricular organs to reach the brain. Cytokines can also reach the brain via active transporters. The researchers focused particularly on the effects of the bacterial endotoxin lipopolysaccharide (LPS) to examine the effects of cytokine activity on depressed mood. Because LPS is a powerful activator of pro-inflammatory cytokines, it was an ideal toxin to study. They noted that LPS induced different sickness behaviors associated with depression, and that this was related to the circulating cytokines in the body (Muller et al., 2011). The use of inflammatory biomarkers and their relation to depression shows the link between the environment, and how that affects the immune system.

Miller, Maletic, and Raison (2009) focused on the pathophysiology of major depression, by describing the relationship between the environment, the brain, and the immune system. They were able to break down some of the major factors involved in the grand scheme of PNI, to illustrate how each aspect of the body communicates with one another:

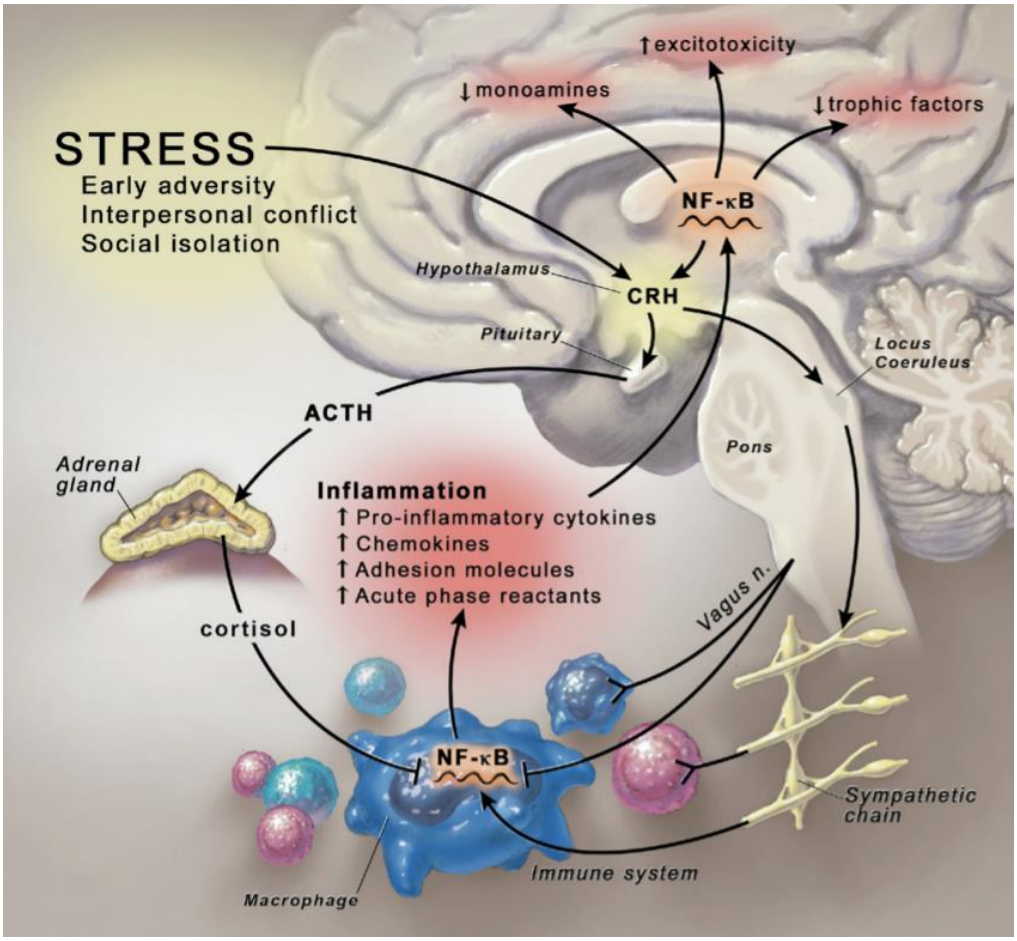

Figure 12. Immune response activation as a result of stress factors (Miller, Maletic, & Raison, 2009).

While PNI is much more complex than what Figure 12 displays, the figure highlights the main anatomical structures and molecules involved in the dynamic of this relationship. As an overview, stress from the environment is introduced to the organism, which stimulates the hypothalamus. The hypothalamus, which is responsible for maintaining homeostasis of the body, secretes corticotropin-releasing hormone (CRH) to stimulate an immune response to stress. This immune response involves an upregulation of several factors, one of them being pro-inflammatory cytokines. Illustrated by the figure, stress

response does not stop at the immune system. As an ensemble, these inflammation factors induce inflammatory signaling pathways in the brain to cause changes to cell activity, and further change stress response (Miller et al., 2009). The overall message to take away from the figure is the complexity of all the networks involved in PNI: how information from the environment is processed within the brain, how the brain sends that information to the immune system, and how the immune system generates an appropriate response to the environmental stimuli.

3.4 Bidirectional Relationship

As shown in previous figures (Figs. 11 & 12), PNI can be seen as a dynamic in which changes to one area of the body cause changes to another. An interesting aspect of this dynamic is that it does not function in one direction, but rather bidirectionally. Emotions can affect mood and cause a wide range of mind states, from elevated states of euphoria to lowered states of depression. Often times life stressors can lead to the development of mood disorders, such as major depressive disorder. Jaremka, Lindgren, and Kiecolt-Glaser (2013) focused on the notion that depression and inflammation is a strong, bidirectional relationship. The researchers first noted how there were both positive and negative correlations between stressor levels and levels of inflammation. For example, people who suffered from major depression expressed increased levels of pro-inflammatory cytokines. On the other hand, their counterparts who were not depressed expressed lower levels. One major example of a life stressor is relationships, a sense of connection. Humans are programmed to seek connection with others in order to feel as a part of society. When an individual begins to feel lonely, this life stressor occurs and inflammation increases in the individual: genes that express pro-inflammatory cytokines

are upregulated, while genes that express anti-inflammatory cytokines are downregulated. As a result, an individual who experiences loneliness can start to display sickness behavior (Jaremka, Lindgren, & Kiecolt-Glaser, 2013).

Interestingly, this relationship between inflammation and depression works in the opposite direction as well. In other words, individuals who have higher levels of pro-inflammatory cytokines greatly experience major depression than those with lower levels. The researchers highlighted the fact that administration of pro-inflammatory cytokines endorsed depression. Subjects who were administered bacterial toxins that exacerbate a pro-inflammatory response started to express somatic symptoms, including less excitement with activity and also a lack of energy – two major symptoms of depression. The researchers suggested that if depression was correlated with increased inflammation, then treatments that aid in reducing depression and stress should lead to a reduction of inflammation. Meditation was found to have benefits with reducing inflammation. Those who practiced meditation more frequently were found to have greater reduction of stress and pro-inflammatory cytokine production than those who practiced less meditation. The results were similar for people who exercised regularly. One important finding to note is that people who do not respond well to antidepressants still produce higher levels of pro-inflammatory cytokines (Jaremka et al., 2013). This supports the idea that there is a strong relationship between psychology and immunology. While it might not be apparent on the outside that stressors do in fact cause illness, it is possible to see the importance of psychological well-being in overall health when dissecting the processes involved on a cellular level.

3.4.1 Neuropharmacological Perspective

Not only can emotions affect the immune system, but the opposite can occur as well: alterations in the immune system can lead to mood imbalances. Neuropharmacological research – such as Haroon, Raison and Miller (2012) – supports the notion that upregulation of cytokine activity can lead to depression. Cytokines are able to access the brain through several mechanisms, including passage through the blood-brain barrier, the use of transport molecules, and even the recruitment of macrophages. Previous studies (Connor & Leonard, 1998; Dantzer, 2001; Maes et al., 1997; Maes et al., 1995; Schiepers, Wichers, & Maes, 2005) have already established how natural upregulation of cytokines can lead to depressive symptoms, but Haroon, Raison and Miller (2012) showed how administration of inflammatory cytokines could essentially induce depressive behavior in the subject. One of the main findings of the study was that chronic administration of the cytokine interferon-α (IFN-α) led to major depression in the treated subjects. When these subjects were compared to medically diagnosed depressed patients, the symptoms between both groups seemed to overlap significantly (Haroon, Raison, & Miller, 2012). The findings show that even an artificial upregulation of cytokines can induce a negative emotional state, which supports the notion of the mind-body connection.

3.5 Behavioral Response

Several cellular and molecular changes occur within the brain and immune system to cause changes to the overall physiological system, but one of the main reasons why PNI is studied is to show the ultimate effect of all these changes due to stress and depression – the organism's behavioral response.

3.5.1 Stress and Behavior

Returning to Lieberwirth et al. (2012), the researchers not only focused on the effects of social isolation on neurogenesis, but they also examined how chronic isolation affected overall behavior of the prairie voles. One aspect of their experiment involved comparing the behaviors of control prairie voles and isolated prairie voles in an open field apparatus (Lieberwirth et al., 2012):

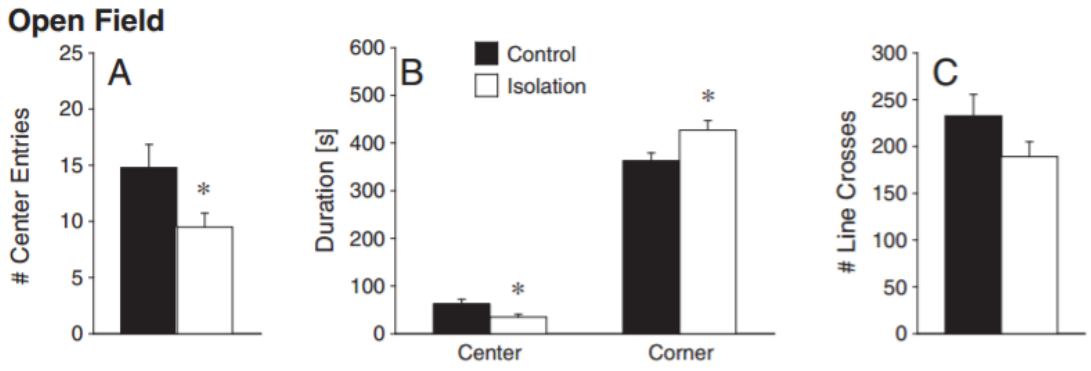

Figure 13. Locomotor activity between control and isolation prairie voles in an open field (Lieberwirth et al., 2012).

The researchers found that while overall locomotor activity was similar between the two conditions (Fig. 13C), the control prairie voles moved to the center of the apparatus several times whereas the isolated prairie voles stayed in the corners more often (Fig. 13A and B). These findings are consistent with the notion that individuals exposed to a normal social setting can be more confident and further be more able to explore their surroundings without feeling vulnerable. On the other hand, individuals exposed to a more stressful social situation (i.e., isolation) may feel more vulnerable and cautious

towards their surroundings, due to feeling neglected and abandoned. This lack of trust creates a helpless state of mind. These findings are consistent with anxiety and depression behaviors, suggesting that negative stressors can greatly impact overall behavior.

Studies demonstrate the detrimental effects of negative emotions on the immune system, by illustrating the increase of inflammation in individuals who suffer from depression and anxiety. In one particular study, three groups were involved – one group included women who were caring for a relative with Alzheimer's disease, and the other two groups included women who were concerned with "housing relocation or community controls" (Kiecolt-Glaser et al., 2002). Although all three groups were preoccupied with highly stressful situations, blood test results in the Alzheimer's group demonstrated significant upregulation of IL-6 in their plasma when compared to the other groups. A remarkable point to make here is that the women in this group were, on average, six to nine years younger than the women in the other two groups (Kiecolt-Glaser et al., 2002). Although it could be assumed that younger individuals are more likely to have a stronger immune system, negative emotions are still able to suppress its strength and lower the immunity of even younger individuals. This demonstrates the significance in the mind-body connection, as stressors that negatively affect the mind also negatively affect the body.

Further evidence shows how negative emotions can indirectly cause hindrances to the immune system, triggering a higher susceptibility to illness. Because negative emotions suppress the defense mechanisms of the immune system via a decrease in anti-inflammatory cytokine activity, individuals are prone to a much slower healing process. Illness is able to persist, which increases health risks and the possibility of developing

disease (Kiecolt-Glaser et al., 2002). One study supports this notion by comparing two groups and their reactions to inoculated vaccinations. The results suggest that when individuals displayed high levels of negative emotions, they were less capable of responding to stronger vaccinations. The researchers related this finding to pathogens, stating that individuals would react similarly when faced with adversity to the immune system. In other words, the immune systems of individuals who were stressed and/or anxious were likely to respond only to weaker pathogens while not being able to fight off stronger pathogens or infectious disease. This evidence reaffirms the strong connection between emotions and homeostatic processes.

CHAPTER 4: CONCLUSION

This research first examines the disciplines within PNI, establishing the three areas of scientific study. After establishing the disciplines, the paper specifies each discipline by investigating the importance of particular structures within each subsystem. These subsystems are then shown to have physical relations with one another, creating interconnecting pathways that interact bidirectionally to create molecular and cellular changes. While stress can cause changes to the brain, which further causes changes to the immune system, alterations to the physiological system can also occur in the opposite direction. This intimate connection between the mind and the body shows the importance of studying PNI. While there is already a lot of literature establishing these important connections, further research is still needed in order to enrich the literature in this field of medical research.

4.1 Future Studies

4.1.1 Focus on the Endocrine System

Although the endocrine system was briefly mentioned in the paper, this aspect of PNI has its own section of literature – psychoendoneuroimmunology (PENI) – that adds to the complex physiological dynamic. The endocrine system consists of endocrine glands and tissues that are responsible for producing hormones. These chemical messengers are released and travel through the bloodstream to specific target organs, allowing these organs to produce a certain physiological response. Each response is involved in regulating certain mechanisms in the body, including metabolism, absorption of nutrients, and even response to stress. Focusing on stressors, it is possible to see how these stressors can disrupt the homeostatic functioning of hormones. As opposed to keeping hormonal levels within relatively safe physiological conditions, hormones are either increased or decreased in concentration, which leads to shifts in endocrine response.

There is a correlation between depression and hormonal activity in the body that suggests how negative emotions can damage physiological regulation. Cortisol, as mentioned before, is a steroid hormone that is produced and secreted in response to stress. Interestingly, cortisol is beneficial when it comes to the fight-or-flight response, however it can quickly become more disadvantageous when an individual suffers from hypercortisolemia. If an individual is emotionally unable to cope with stress, their response becomes harmful to their physical well-being. Researchers report that stressors, especially those that are unpredictable or out of an individual's control, are linked to increased levels of stress hormones. Interestingly, even if an individual is exposed

repeatedly to the same stressor, they will still exhibit high cortisol levels (Kiecolt-Glaser et al., 2002). Furthermore, cytokines manipulate responses in the endocrine system by stimulating hormone production, which promotes a cascade of hormonal responses. Cortisol levels increase, which can sustain sickness behavior if the high concentration persists (Kiecolt-Glaser et al., 2002). This relationship between depression and cortisol demonstrates the extensive nature of the mind-body connection in the overall physiological system.

4.1.2 Research in Children

O'Connor, Moynihan and Caserta (2014) focused on the relevance of PNI in children in order to examine the relationship between the nervous system and the immune system in a developing body. While PNI had already been established as a scientific approach to examine how different areas of the body interact with one another to produce a response, not much has been done to study damage in a developing individual, and how a young and growing body responds to such damage. The researchers focused on children with neurodevelopmental disorders (e.g., autism) to see how these neural developments could impact overall immune response. The researchers found that children who suffered from such disorders were prone to developing abnormalities in immune function. Not only did they study how the nervous system could affect the immune system, but the researchers also looked at these developments in the opposite direction. That is, they focused on how abnormalities in immune function could affect neural development. The researchers noted that children who suffered a streptococcal infection developed a sudden onset of obsessive-compulsive disorder (OCD), or even Tourette Syndrome (O'Connor, Moynihan, & Caserta, 2014).

The detrimental effects that both neural and immune abnormalities can have in children suggest the importance of studying PNI, in order to develop the research and learn more about the delicacy and critical nature of human pathophysiology. Even though stress and illness are common in adults, and both physical and mental well-being are important to attain, it is also important to focus on the health of children. While youth is generally associated with strong health, certain studies suggest that this may not always be the case.

4.2 The Big Picture

After reviewing the physiological mechanisms behind how stress and depression affect the body's nervous and immune systems, and how neurobiological or immune dysregulation increases sickness behavior, it is important to examine the extent to which stress causes aversive physiological effects and how such effects can exacerbate psychological response. While chronic stressors tend to be damaging towards the body's physiological response, acute stressors actually have an opposite effect (Dhabhar & McEwen, 1997; Miller & Raison, 2016). Studies have shown how acute stressors initiate a boosted immune response that is able to easily fight off pathogens, or quickly repair damaged tissue, depending on the situation (Lewis et al., 2008). An acute amount of stress could actually be beneficial to an individual and their response to this type of stressor. Because the periodic length of acute stress is not extensive as it is in the case of chronic stress, the body is able to fight off the pathogens responsible for the aversive stimuli. However, when a stressor becomes chronic and its damaging effects within the body are prolonged, the physiological response becomes harmful to the individual's

overall health. Chronic stressors lead to suppression of the anti-inflammatory response, making it difficult for an individual to properly respond to such a stressor.

Extensive neurobiological and immunological damage can also cause an increase in depression and sickness behavior. As examined throughout the paper, it is possible to see how damage to the body can contribute to negative psychological changes. Alterations to the HPA axis and hippocampal neurogenesis have been linked to difficulties with adapting to stress. Seemingly minor changes to receptor activity in the brain, as well as changes to neuronal wiring, suggest that these neurobiological aspects of the brain are actually more significant in affecting overall behavior. The immune system has been shown to have substantial effects on depressive symptoms as well, due to its delicate homeostatic nature. Slight changes to immune response can greatly affect behavior, inferring that this subsystem also has a strong connection to sickness behavior. The bidirectional nature of the mind-body connection supports the notion that both mental and physical well-being must be present in order to achieve overall well-being.

Although the amount of PNI research is still not as extensive as other fields of medicine, there is still strong evidence that there is an intimate relationship between the mind and the body. Some research on happiness and its effects on the physiology of the body demonstrate opposite effects when compared to the evidence that was presented in this current study. Further studies on happiness and other emotions in the spectrum could help enhance the notion that mental health is a crucial aspect of life. Although issues that congregate within the mind are not visible and objective to the outside world, these issues are still critical when it comes to an individual's entire well-being. Without mental health, physical health becomes even more difficult to achieve. This field of research

continues to pioneer a new view on health and well-being, and provides a better understanding on the physiological psychology of how the mind truly connects to the body.

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