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Looking Back to Move Forward: Research in Stress, Behavior, and Immune Function

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Abstract
Background: From the original studies investigating the effects of adrenal gland secretion to modern high-throughput multidimensional analyses, stress research has been a topic of scientific interest spanning just over a century. ***Summary:*** The objective of this review was to provide historical context for influential discoveries, surprising findings, and preclinical models in stress-related neuroimmune research. Furthermore, we summarize this work and present a current understanding of the stress pathways and their effects on the immune system and behavior. We focus on recent work demonstrating stress-induced immune changes within the brain and highlight studies investigating stress effects on microglia. Lastly, we conclude with potential areas for future investigation concerning microglia heterogeneity, bone marrow niches, and sex differences. ***Key Messages:*** Stress is a phenomenon that ties together not only the central and peripheral nervous system, but the immune system as well. The cumulative effects of stress can enhance or suppress immune function, based on the intensity and duration of the stressor. These stress-induced immune alterations are associated with neurobiological changes, including structural remodeling of neurons and decreased neurogenesis, and these contribute to the development of behavioral and cognitive deficits. As such, research in this field has revealed important insights into neuroimmune communication as well as molecular and cellular mediators of complex behaviors relevant to psychiatric disorders.

Historical Introduction of Stress

The wonder of the human mind – that which governs the rest of the body – has enchanted and puzzled philosophers and scientists for millennia. One experience of great interest is stress – the familiar feeling one gets when faced with a challenge. Despite the widespread public use of the term "stress," it is usually described vaguely and ambiguously. For example, it can refer to the event (stressor) or the response (stress response) [1]. As once described by Hans Selye, the man who coined the term, "everybody knows what stress is and nobody knows what it is" [2]. To start our historical review, it is best for us to start at the turn of the 20th century. Many of the important events discussed in this review are summarized in a timeline presented in Figure 1.

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In 1884, an article by the American philosopher and psychologist William James posed an interesting question: "Do we run from a bear because we're afraid or are we afraid because we run?" [3]. James poses the idea that physiological changes directly follow the perception of external stimuli, and the sum of these internal changes is the experienced emotion. This is the basis of the James-Lange theory of emotion [4]. This assertion was met with much scrutiny by the American physiologist Walter Cannon, who through his experiments on severing afferent nerves of the sympathetic division and assessing emotional response argued that the feeling of emotion and the physiological changes that occur in response to external stimuli are independent of one another [5]. In the same work, Cannon coined the term "fight-or-flight" to describe the state an animal goes into when challenged with a threat. This state is marked by physiological changes such as increased heart rate, ventilation, piloerection, and decreased digestion. Cannon later went on to establish the idea of homeostasis [6], in large part based on Claude Bernard's work describing the constancy of the "milieu interior" or "internal environment" of the body (first event on Fig. 1 timeline) [7]. In this article, Cannon emphasizes the role of the autonomic nervous system (ANS) in keeping constant the factors of the interior environment and how changes in the external environment excite reactions in this system and lead to disturbances.

In the 1930s, the Hungarian-Canadian endocrinologist Hans Selye was conducting experiments to identify female sex hormones. These studies involved the injection of various extracts into female mice. Curiously, all the extracts produced the same results: adrenal gland growth, thymic involution, and peptic ulcers in the stomach and duodenum. Selye continued experiments on female mice but instead of injecting them with various extracts, he exposed them to stressful situations such as cold exposure or forced running on a wheel. These additional experiments yielded the same effects, leading Selye to conclude that this syndrome arises from the animal attempting to adapt to the changing conditions. He called these combined effects the general adaptation syndrome (also referred to as Selye's syndrome) and organized it into three distinct phases (see top-right corner of Fig. 1): the alarm phase, the phase of resistance, and the phase of exhaustion [8]. He later renamed general adaptation syndrome as the "stress response," or more simply "stress," borrowing the term from physics and inserting it into the medical lexicon [9]. Selye continued to make further advancements in the newly established field of stress research by describing information "mediators" between the brain and peripheral organs [10], comparing the differences between healthy stress ("eustress") and pathogenic stress ("distress") [11], and began to link stress biological pathways with immunology [12].

Discovery of Stress Hormones and Their Neurobiological Effects

The hormones secreted from the adrenal glands were known to be necessary in facilitating physiological responses as far back as Cannon's work [13, 14], but the steroid compounds were not formally isolated from the adrenal cortex until the 1930s through the efforts of competing scientists and eventual 1950 Nobel laureates, Edward Kendall and Tadeusz Reichstein (Fig. 1) [15]. Cortisol, called "compound F" by Kendall, was synthesized a decade later [16]. All steroids secreted by the adrenal gland would come to be known as corticosteroids, which itself was broken into two classes: glucocorticoids (GCs) and mineralocorticoids, also named by Selye [15, 17]. Of note, it was Selye who emphasized that the stress response is not solely due to the systemic release of adrenaline and noradrenaline (catecholamines) from the adrenal medulla but also the systemic release of cortisol (GC) from the adrenal cortex that plays a role in the stress response [18]. Nearly 40 years later, GC release was found to be controlled by communication between the hypothalamus, pituitary gland, and adrenal gland. These insights established the field of neuroendocrinology and initial conceptualization of the brain-body connection known as the hypothalamic-pituitary-adrenal (HPA) axis [19–21].

Later, the American neuroscientist Bruce McEwen connected the stress response to brain regions previously associated with memory and cognition. His seminal work in the 1960s (see middle section of Fig. 1), through the use of radioactive corticosterone, showed a high presence of glucocorticoid receptors (GRs) in the rat hippocampus [22]. He and his colleagues would go on to show further retention of GCs in other rat brain regions [23], as well as the hippocampus of nonhuman primates [24]. Around this same time, estrogen (another steroid hormone) was found to bind to intracellular receptors and enact transcriptional changes in various tissues leading to morphological changes [25]. These breakthroughs led to an exciting question – could steroid hormones such as GCs produced during stress influence the structure and function of neurons, and consequently entire brain regions?

A plethora of studies looking into how stress and GC signaling affect neuronal structure within multiple brain regions were published in the 1990s–2000s (see Fig. 1). Early studies linking GC levels and memory loss in

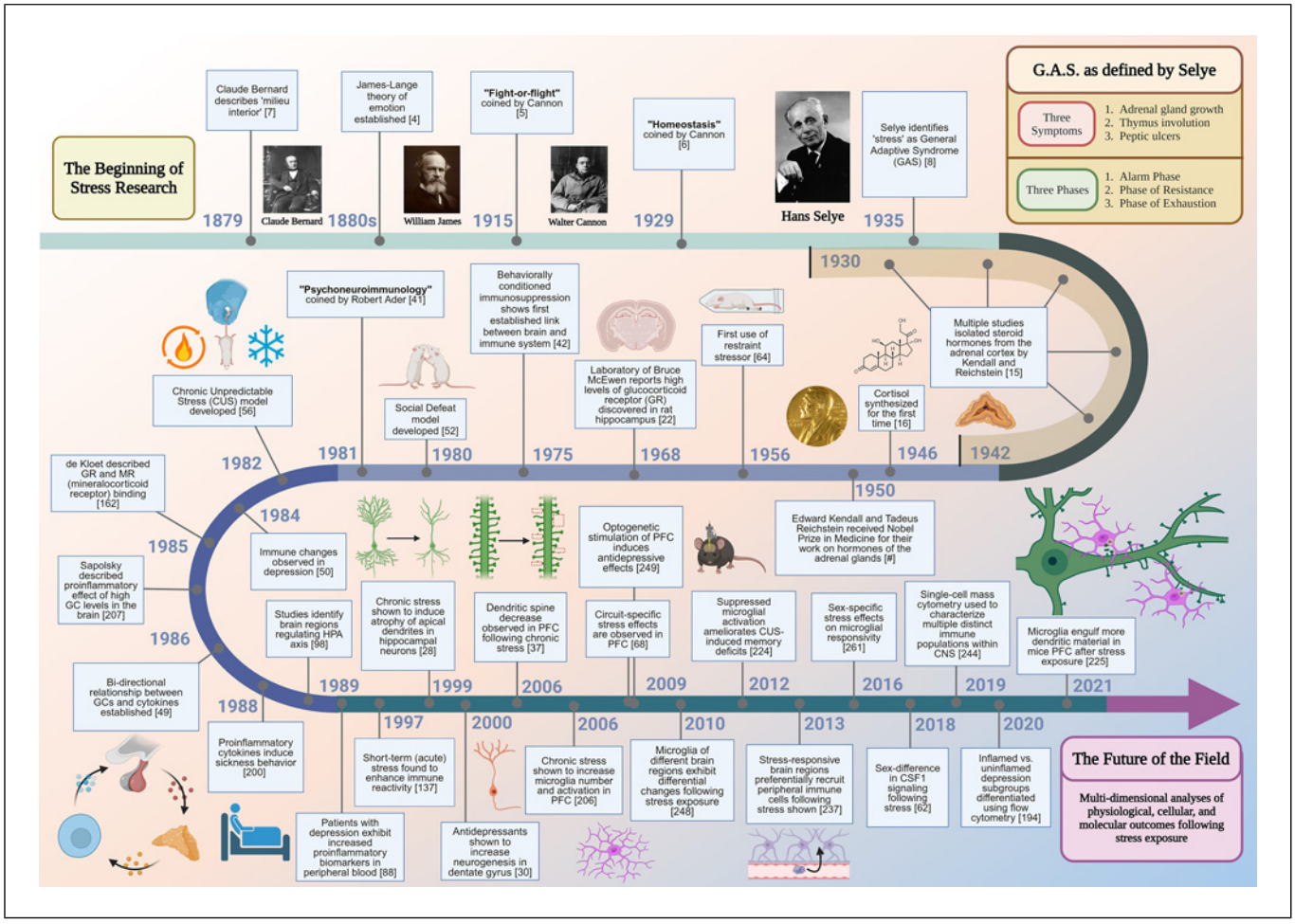

Fig. 1. Timeline of prominent events and findings in stress research (1879–present).

hippocampus [26] directed investigators to analyze the structure of pyramidal neurons in the CA1, CA3, and dentate gyrus [27–29]. These studies revealed that stress caused dendritic retractions in pyramidal neurons of the CA1 and CA3 regions and reduced cell counts within the dentate gyrus – demonstrating a reduction in adult neurogenesis. Intriguingly, antidepressants were found to increase neurogenesis in the same region, linking depression and stress with overlapping neurobiological alterations [30]. Other studies showed that patients with psychiatric disorders such as depression or post-traumatic stress disorder (PTSD) exhibit reduced hippocampal volume [31, 32] which incorporated the hippocampus into brain regions associated with mood disorders. Further studies revealed that the prefrontal cortex (PFC) also had high levels of GRs [33]. As such, exposure to chronic stress caused dendritic retraction of PFC pyramidal neurons as well [34–36]. Dendritic spines were also shown to decrease on pyramidal neurons of the PFC following stress exposure, with the largest deficits rising in the most distal sections of the apical dendrites residing in layer I [37]. In contrast, the amygdala, which is reciprocally connected to the hippocampus and PFC [38], exhibited an expansion of dendrites following stress exposure [39]. The orbitofrontal cortex also exhibited dendritic expansion following repeated stress [35]. One potential cause in the differential stress response between these regions may be differences in expression of neurotrophic factors such as brain-derived neurotrophic factor following stress exposure [40].

The Beginnings of Psychoneuroimmunology

The impact of stress responses on the immune system and disease was recognized by the American psychologist Robert Ader and American microbiologist Nicholas

Cohen. Before their work, it was widely believed that the immune system was autonomous – strictly independent of the nervous system [41]. In a study that was initially investigating taste aversion, rats were subjugated to injections of cyclophosphamide, an immunosuppressing agent, after they drank from saccharine-water solution to condition them to avoid the sweetened water [42]. After sufficient conditioning, Ader and Cohen force-fed the rats the saccharine-water without injection of cyclophosphamide to simply complete the experiment properly with extinction trials. What they did not expect was the sugary water alone elicited a rather severe reaction leading to the death of multiple rats. Ader and Cohen hypothesized that avoidance was not the only thing conditioned but also the immunosuppressive effects of cyclophosphamide, effectively establishing a functional connection between the brain with the immune system. This work was foundational for the beginning of an emerging new field called psychoneuroimmunology – a term coined by Ader himself who would first use it in a speech to the American Psychosomatic Society in 1980 (Fig. 1) [41]. This paved the way for breakthroughs in the late 1970s and 1980s that showed inflammation could alter neuronal signaling in the hypothalamus [43] and bidirectional communication between the brain and the immune system [44, 45]. Further studies showed how stress could alter the immune system [46, 47] and increase susceptibility to physical illness [48]. Specifically, cytokines can engage in neuronal communication regulating GC release, and GCs can subdue further cytokine release [49]. Concurrently, other studies were finding immune abnormalities within patients diagnosed with major depressive disorder (MDD) [48, 50] or schizophrenia [46], laying the groundwork for further studies investigating the relationship between the immune system and complex brain disorders.

Preclinical Models of Stress

To study stress and its associated cluster of stress-related psychiatric disorders, a multitude of preclinical rodent models have been developed [51]. They can be categorized based on the type of stressors they employ (physiological, psychological, or both) and/or the duration of the model (acute vs. chronic). Examples of commonly used rodent stress models are the social defeat paradigm, chronic unpredictable stress (CUS), restraint stress, and early-life stress (ELS).

The social defeat paradigm is a physiological and psychological model that involves an intruder Sprague-Dawley rat being attacked (defeated) by resident Long Evans rats over the course of multiple days [52]. After being defeated, intruder rats are confined in the same cage as their attackers with only perforated plexiglass separating them, allowing for intense visual, olfactory, and auditory stimuli to affect the defeated rat. This paradigm is proposed to mimic human stressors such as aggression, bullying, and chronic subordination that contribute to the development of PTSD [53]. Social defeat stress has been shown to promote social avoidance and induce increases in pro-inflammatory cytokines and blood-brain barrier dysfunction in mice, which recapitulate some features of psychiatric conditions [54, 55].

CUS uses multiple randomized physiological and psychological stressors to avoid acclimation. When first developed in the early 1980s (as shown in Fig. 1), experimenters primarily used physiologically related stressors involving pain (shock exposure), hunger (food deprivation), thirst (water deprivation), and exposure to noxious conditions such as extreme heat [56]. In 1987, modifications to include more natural and milder stressors were used to better simulate the continued mild stress in which humans might endure [57]. These stressors included by Willner were wet (soiled) bedding, tilted cage, radio noise, constant lighting, and strobe light exposure. Nonetheless, it is important to note to the reader that laboratories often employ unique combinations of these stressors and for various timespans [58]. Other names have been given to this paradigm such as chronic variable stress [59] and chronic mild stress [58] – but it should be stated clearly that these all describe the same practical experimental set-up [60]. CUS is model aspects of psychiatric disorders as the regiment has been shown to induce passive coping behavior, working memory deficits, and synaptic loss [61, 62].

Restraint stress, originally devised in France to study interactions between the nervous system and gastrointestinal tract (see Fig. 1) [63, 64], is a stressor in which the animal is restricted to a small space in which they are unable to move freely for a set period of time and this duration varies from experiment to experiment [65]. Intriguingly, anxiety-like and depressive-like behaviors are more repeatably and reliably observed in chronic restraint paradigms (>6 days) [66]. This regimen was used to show that hippocampal CA3 neurons undergo atrophy of their apical dendrites following stress [67]. Of note, repeated stress was used to discover circuit-specific effects of stress on neuronal morphology in the infralimbic region of the PFC, emphasizing that neurons with different efferent projections can have divergent stress effects [68]. Interestingly, shortened versions of this regimen (5 min daily) have been shown to reverse stress-induced behavioral deficits from longer versions

(2 h daily), showing the potential adaptive features of acute stress [69].

All the models listed previously involve stress exposure in adulthood. However, data have shown that exposure to stressful events early in life can have long-lasting consequences, such as higher risk for development of depression, anxiety, and cognitive impairments [70, 71]. Also, clinical data suggest that exposure to ELS (i.e., childhood trauma) increases circulation of inflammatory biomarkers [72]. In order to model childhood adversity or trauma, most ELS models employ a method where parental/maternal care is reduced, because the parent-child relationship is the source of most early-life interactions [73]. Two models that manipulate this relationship are intermittent maternal separation (MS) [74, 75] and limited nesting and bedding material [76, 77]. MS involves keeping mice separated from their mothers and their nest for 3 or more hours a day over the first two postnatal weeks [74] which leads to increases in depressive-like and anxiety-like behaviors [78] and alterations in HPA axis activity [79]. Intriguingly, "handling" or shorter bouts of separation from the mother (15 min daily) result in opposite effects of MS [78]. Limited nesting and bedding involves limiting nesting material for the mother to build a nest for her pups [76] which leads to a myriad of stress-related effects across many mouse lines [80], including elevated corticosterone levels [81] and altered exploratory and coping behaviors in various tests [82, 83].

Components of the Stress Response: The ANS and the HPA Axis

Research in the field of stress has demonstrated that physiological and neurobiological systems are important for adapting to stress. Exposure to stressful stimuli and perception of threat activate two systems within the body, the ANS and the HPA axis [84]. These systems function as survival mechanisms and ready the body to respond to the dangers at hand. McEwen developed the construct of "allostatic load" to describe the long-term effect of the physiological response to stress, applying the concept of allostasis to stress theory. Allostasis is defined as stability through change. He postulated that the accommodation the body makes via the autonomic system and HPA axis to protect the body from internal and external stress can result in wear and tear either through chronic overactivity or underactivity of the aforementioned neurobiological systems [85]. Correlations were found between stressful life events and an increased disposition to develop psychiatric conditions such as depression, PTSD, and anxiety disorders which researchers refer to as "stress"-related psychiatric disorders [85–87].

Further studies of the body's stress response have made it apparent that many other systems are affected after exposure, one of them being the immune system [88, 89]. Both the HPA axis and the ANS act as extensions of the nervous system, directly influence the function of the immune system, and affect immune changes throughout the body. Under normal conditions, the body only encounters stressful situations every now and then; however, certain conditions can lead to persistent or chronic stress. Understanding the connection between chronic stress and immune system activation is important because dysregulation of either part can lead to the development of neurobiological deficits associated with psychiatric disorders [90, 91].

The Role of the ANS in the Stress Response

The ANS functions to regulate involuntary actions of the nervous system. At the most basic level, this system controls the body's ability to switch between a state of "alertness and responsivity" and a state of "rest and maintenance." These two opposing states are mediated by innervating systems called the sympathetic nervous system (SNS) and parasympathetic nervous system (PNS), respectively [92], and they can produce systemic changes through its extensive innervation of most tissues and organ systems in the body [93]. Neurons and nerves within these systems potentiate signals through the release of either noradrenaline or acetylcholine neurotransmitters. Since both systems are tonically activated, input from either can increase or decrease, and often have opposing effects. Simultaneous increase in the activity of one system and decrease in the activity of the other allow the ANS to quickly change the body's state in response to threats. Therefore, the ANS is the first line of defense in a situation where stress is encountered [94].

One example of the body's response to stress is a rapid increase in heart rate and blood pressure. This is driven by sympathetic projections that increase activation of cardiovascular tissues such as the heart and blood vessels [93]. Other effects of increased sympathetic activation are sweat secretion, dilation of blood vessels within skeletal muscle, and constriction of blood vessels within the gastrointestinal tract. All these actions work to direct energy to the parts of the body that would need to respond in the event that there is a threat to survival. These effects as described here are carried out by direct

projections to the target tissue; however, the SNS can also induce these effects indirectly through projections to the inner part of the adrenal gland called the adrenal medulla. The cells inside the medulla produce adrenaline which is secreted and picked up by the circulating blood. This allows for transmission of adrenaline to the different target tissues throughout the body [94], amplifying the effects of SNS activation.

The Role of the HPA Axis in the Stress Response

The HPA axis is an endocrine network in the body that shapes the stress response by optimizing energy utilization. While the ANS and HPA axis have different roles in the stress response, they both ultimately work to prepare the body to respond to the stressor. One difference is that the ANS responds to a stressful situation within seconds and its activation is relatively short, whereas the HPA axis responds more gradually and persists beyond the initial activation [94, 95]. This is due in part to the anatomical location of the components and because the signals must travel between parts of the axis through the bloodstream. In particular, the signaling cascade is initiated in the hypothalamus, an area of the brain that receives input from the brainstem and is activated by signals of homeostatic imbalance. Sympathetic neurons within the brainstem project to and excite neurons in the hypothalamus, leading it to secrete corticotropin-releasing factor (CRF) that acts on the pituitary gland and signals the secretion of adrenocorticotropic hormone (ACTH) [96]. The pituitary is connected to the circulatory system, so once the secreted hormone, ACTH, enters the bloodstream, it is transported throughout the body. Once it reaches the adrenal gland, it works to stimulate the synthesis and release of GCs from the outer adrenal cortex. Interestingly, activation of the HPA axis does not necessarily require stimulus from sympathetic neurons and can be activated by both real and predicted threats. The response to a predicted threat is the body anticipating homoeostatic imbalance and can be triggered by species-specific innate fear or through conditioning and memory [97]. Many of the nodes of the HPA axis can be inhibited or stimulated by other brain regions, such as the hippocampus (see Fig. 1) [98, 99], PFC [100], and amygdala [101, 102]. Generally speaking, the hippocampus and PFC inhibit HPA activation and the amygdala stimulates HPA activation [103] but there are differences within subregions.

Through pharmacological experiments, scientists have shown that HPA axis activation during acute stress and subsequent GC release induces preparation of stored energy reserves for use and inhibition of glucose (energy) use in peripheral tissues [104]. This is important for the body to be prepared to expend energy and act in response to any threats presented by the stressful situation. One of the most important functions of GCs (most notably, cortisol) is regulation of their own secretion at multiple junctures in the HPA axis through negative feedback mechanisms [105]. Cortisol has been shown to inhibit production of both CRF from the hypothalamic paraventricular nucleus (PVN) [106, 107] and ACTH from corticotroph cells of the anterior pituitary [108, 109]. Also, cortisol can act directly on steroidogenic cells within the zona fasciculata of the adrenal cortex. It is been shown both in vitro and in vivo that GC presence in the adrenal gland can limit ACTH-induced cortisol synthesis and release of GCs [110, 111]. GR is present within these cells, suggesting a local feedback mechanism driven by activated GR translocating into the nucleus and modulating expression of genes regulating steroidogenesis and cytoskeleton reorganization [112, 113]. These mechanisms govern the homeostatic balance of HPA axis activity and facilitate the basal vicissitudes of GC secretion in the body.

The HPA Axis and Circadian Rhythm

The circadian rhythm is another important factor that controls HPA axis activation. Similar to other hormones, GC release follows a cyclic pattern with peak GC concentrations observed at the onset of the active period (i.e., early morning for diurnal animals, just after sunset for nocturnal animals) and the trough observed at the onset of the inactive period (i.e., just after sunset for diurnal animals, early morning for nocturnal animals). These rhythms are regulated by "master clock" systems that include light-sensitive neurons in the retina and the suprachiasmatic nucleus (SCN) of the hypothalamus. Neuroendocrine cells in the SCN project to and stimulate the CRF/arginine-vasopressin-containing neurons of the PVN to secrete CRF [114], activating the HPA axis cascade described previously in this review. In addition, SCN neurons can modulate the sensitivity of the adrenal gland to ACTH via its connection to preautonomic neurons of the PVN [115]. Studies transecting splanchnic nerves observed adrenal glands with decreased sensitivity to ACTH, implicating the nerve in this pathway [116].

Reciprocally, cyclic GC release facilitates the synchronization of intrinsic molecular patterns. GCs have been found to regulate transcription of clock proteins

within peripheral tissues [117], immune cells [118], and neurons in the PFC [119], hippocampus [120], and amygdala [121]. Furthermore, the time-of-day-dependent fluctuations in GC levels in these brain regions lead to changes in formation and elimination of dendritic spines on neurons [122, 123]. These findings provide evidence that GCs are critical mediators of neuron function and behavior across the circadian cycle [124]. Intriguingly, GC feedback to the SCN appears to be promoted by astrocytes [125], as SCN neurons of adult rodents are some of the few cells that do not express GR [126].

With the integrated physiological actions of circadian rhythm and HPA axis, it may come as no surprise that disruptions of the circadian rhythm are associated with altered HPA axis activity and stress-related psychiatric disorders. For instance, reduced clock gene mRNA was observed in postmortem PFC tissue of patients with MDD [127] and abnormal diurnal cortisol patterns were observed in patients with PTSD [128]. Other studies have linked both knockdown of the clock protein and chronic stress with disruptions in mood-related behaviors [129, 130].

Stress Interactions with the Peripheral Immune System

The tie between the nervous system and the immune system most likely arose as an evolutionary mechanism, as historical stressors were likely more physically threatening and may have resulted in injury. In this context, activation of the immune system following stressor exposure allows the body to prepare an immune response to any wounds inflicted and likely would have promoted survival of the organism [131–133]. To that point, short-term stress can mobilize immune cells to enhance innate and adaptive immune responses. For example, acute stressors have been shown to traffic and redistribute leukocytes from the blood to organs like the skin, lymph nodes, and bone marrow [134, 135], and this enhanced immunity in those organs [136]. Interestingly though, when stress becomes chronic, it has the paradoxical effect of suppressing the immune system. Indeed, a paradigm-shifting study conducted by Dhabhar and McEwen analyzing an immune response in the pinnae of rats after stress exposure showed that while acute stress increased the redeployment of blood lymphocytes to the pinnae, chronic stress produced the opposite effect – a decrease in the number of blood leukocytes trafficked to the pinnae [137]. Reinforcing Selye's concept of eustress and distress, this study led to a more nuanced understanding of stress effects on immune function in which short-term stress enhances immune reactivity and long-term (chronic) stress diminishes immune responsivity. It was later found that chronic stress also leads to dysregulation of cytokines and related immune responses [138, 139]. So, it has been proposed that the effect of stress on the immune system is dependent on the type and duration of the stressor [137, 140]. In this context, it is important to define how individual components of the stress response (i.e., the ANS and the HPA axis) contribute to differing effects on the peripheral immune system.

ANS Effects on the Peripheral Immune System

Neuroanatomical studies of innervation of the immune system have demonstrated that the ANS directly interacts with immune organs, including the thymus [141], spleen [142], lymph nodes [143], and bone marrow [144]. This is mainly regarding the SNS, as no evidence has been found for PNS innervation of immune organs. Those studies have shown that there are direct sympathetic projections to all primary and secondary immune organs [145], and it is through these conduits that the SNS enacts its effects on the peripheral nervous system via release of catecholaminergic neurotransmitters [146]. Meanwhile, the PNS drives its effects on the peripheral immune system primarily through stimulation of the vagus cranial nerve [147]. When stimulated, acetylcholine is released by the efferent arms of the vagus nerve and binds to cholinergic receptors on macrophages, inhibiting cytokine release [148]. Interestingly, the afferent arms of the vagus nerve respond to fluctuations in peripheral cytokines, such as tumor necrosis factor (TNF), acting as a sensor of peripheral immune changes [149]. The combination of the afferent and efferent vagal fibers creates a vagal-immune connection called the cholinergic anti-inflammatory pathway [150, 151].

Stress has been shown to alter both arms of the ANS. In terms of the SNS, chronic stress increased innervation of the paracortex of lymph nodes and increased acceleration of immunopathogenesis [152]. Bone marrow production of pro-inflammatory monocytes and myeloid-derived suppressor cells has also shown to be upregulated with chronic stress – another SNS-induced stress effect [153, 154]. Acute stress has also been shown to cause changes in immune cell distribution throughout the periphery. One study in mice subjected to experimental autoimmune encephalomyelitis showed a reduction of leukocytes in

the lymph nodes as well as an increase of leukocytes in bone marrow following acute stress [155]. When it comes to the PNS, it was found that acute restraint stress was able to protect mouse kidneys from ischemia-reperfusion injury via the cholinergic anti-inflammatory pathway and that C1 neurons of the medulla oblongata were required for this protective effect [156]. These studies highlight not only the wide effects stress can have on the periphery, but the importance that the duration has on the outcome (acute vs. chronic).

HPA Axis Effects on the Peripheral Immune System

Another function of GC release during chronic stress involves regulating aspects of peripheral immunity. Historically, GCs have been characterized as primarily anti-inflammatory in nature because they are capable of inducing apoptosis of some immune cells, and synthetic GCs have been successfully used to treat autoimmune disorders for many years [157]. Some other examples of the suppressive nature of GCs include their ability to inhibit antigen presentation and reduce proliferation of B cells [95]. However, even though evidence has found an anti-inflammatory role for GCs, evidence to the contrary has been found. In some contexts, they can increase the likelihood of survival of some immune cells [95, 134, 158]. Initial findings suggested that GCs suppress maturation (negative selection) of T lymphocytes, but further studies showed that they can also promote maturation of T cells (positive selection) by working in concert with other mechanisms of T-cell selection [159]. As previously mentioned, short-term stress (or short-term increase in GC secretion) can increase immune reactivity, while chronic stress (persistent increase in GC secretion) can dampen immune responses [136, 137]. This is supported by studies looking at varying levels of GCs; it appears that it can have opposing roles depending on the concentration administered and the duration of the administration [95, 160, 161].

GCs mainly enact their effects via binding to GRs or mineralocorticoid receptors (MRs) [162] which are expressed by most cell types in the body [163]. Both GR and MR are nuclear receptors, meaning after they are bound by GCs, they translocate to the nucleus to regulate gene transcription [164]. Activated GR can exert anti-inflammatory effects through transcriptional regulation of immune-related genes containing a GC regulatory element [165]. Another means by which GR can regulate immune-related transcription is by interfering with pro-inflammatory transcription factors such as nuclear factor-κB and activator protein 1 (AP-1) in a process called tethering [166]. It should be noted that not all GC-mediated effects are genomic [167]. Non-genomic effects of GCs such as changes in intracellular calcium and activation of kinase cascades (MAPK, ERK, etc.) are regulated by membrane-associated GRs and MRs [168, 169]. Through these mechanisms, GCs can direct cell-type-specific effects that lead to alterations in both the innate and adaptive immune systems [170, 171].

This review has extensively covered the effects of GCs secreted from the adrenal gland following HPA axis stimulation, but the adrenal gland can release other soluble factors that regulate immune function, namely, cytokines. Early studies revealed that stress elicits the production of interleukin (IL)-18, also known as interferon-ɣ-inducing factor, in the adrenal cortex, which directly impacts innate and adaptive immune responses [172–174]. The inactive form of IL-18 is constitutively synthesized in a variety of cell types including cortical cells in the zona fasciculata of the adrenal gland [175, 176]. Upon processing primarily done by caspase-1 [177, 178], the mature and biologically active form of IL-18 can be secreted to bind to IL-18 receptors on target cells. IL-18 receptor signaling is primarily pro-inflammatory as it stimulates NK-κB-dependent transcription [179]. After stress exposure, levels of IL-18 and caspase-1 have been shown to increase in the adrenal gland as well as in circulating serum levels, suggesting HPA activation leads to production and secretion of IL-18 from the adrenal gland [180]. Heightened systemic IL-18 levels are not only observed following stress, but in patients diagnosed with MDD as well [181, 182]. These changes in IL-18 signaling may contribute to stress-related changes in cytokines, which will be discussed in subsequent sections.

Stress, Depression, and Cytokines

Alongside the establishment of multiple neuroimmune pathways in the 1990s and 2000s [183], evidence began to show that chronic and severe stress is associated with altered levels of cytokines such as IL-1β, IL-6, TNF alpha, and C-reactive protein (CRP) in blood and cerebrospinal fluid samples [184, 185], and that these changes corresponded with behavioral and cognitive deficits [186]. Multiple studies have shown that many of these same cytokines are shown to be increased in patients with stress-related psychiatric disorders such as depression [187, 188] and PTSD [189, 190].

The first group to study this discovered a correlation between cytokine levels in the blood and reduced

hippocampal volume in patients with MDD [191], which is interesting considering that high levels of cortisol or inflammatory cytokines have been shown to impair neuroplasticity in the hippocampus. This work led scientists to perform clinical studies testing anti-inflammatory interventions for MDD treatment. Initial studies using infliximab (anti-TNF) [192] and celecoxib (NSAID) [193] showed modest effects, but post hoc analyses suggested that those with higher levels of CRP had higher response rates. Another more recent clinical study subcategorized the depressive patient group into the "inflamed depression subgroup" and the "uninflamed depression subgroup." They observed that depression was more severe in the inflamed subgroup and these patients exhibited increased numbers of several immune cell subtypes (i.e., monocytes, CD4+ cells, neutrophils) as well as increased CRP and IL-6 [194]. This evidence all suggests that not only is immune dysfunction connected to chronic stress, but that it may be implicated in the pathophysiology of depression [195].

Stress Effects on Neuroimmune Function

As discussed above, initial studies examined peripheral immune cells because these samples were readily accessible. However, with advances in preclinical models and experimental methods, the field began to examine stress effects on immune function in the brain. Preclinical studies have found evidence that behavioral and cognitive changes caused by stress can be prevented via block of CNS cytokine activity [196, 197]. This work builds on seminal studies that demonstrated immune responses to infection drive behavioral alterations, namely, "sickness behavior" [198–200]. These studies have guided emerging theories that link dysregulation of peripheral and central immune systems in the etiology of psychiatric disorders, particularly MDD [91, 201]. These connections provide the impetus to study how stress affects immunity in the brain and determine if it is involved in the link between immune dysfunction and psychiatric disorders.

Stress-induced dysregulation of neuroimmune function is in part due to the effects of GCs in the brain. As stated above, these bind to both GRs and MRs. The fact that GR and MR have opposing actions explains the inverse U shape of GR action in which intermediate (basal) levels of GCs have opposite results from the extreme ends (no GC and high GC). For instance, acute stress levels of GCs were sufficient and necessary to limit damage following LPS infusion into the brain [202] showing that the basal levels of GCs following acute response are anti-inflammatory in nature [203]. Strikingly, this effect is reversed in chronic stress or high GC concentrations as GCs appear to exacerbate cytotoxic inflammation following either physiological stress [204, 205], psychological stress [206], or prolonged exposure to high levels of GCs [207]. Timing can also determine whether GCs promote pro- or anti-inflammatory effects, as it was shown that if stress-like levels of corticosterone are delivered prior to LPS administration, the immune response (e.g., IL-1β, TNF alpha, IL-6 cytokine release) is enhanced in the hippocampus. However, if the stress-like levels of corticosterone are delivered after LPS administration, the immune response is reduced [208].

Microglia are brain-resident macrophages with diverse functions such as surveilling the CNS for pathogens and maintaining homeostasis through interactions with neurons, astrocytes, and oligodendrocytes [209]. Originally thought to switch between a ramified "resting" state and an ameboid "activated" state, recent studies have shown heterogenous phenotypes in various contexts, reflecting the highly dynamic nature of microglia [210–212]. Stress exposure leads to changes in many aspects that cause microglia to respond as they attempt to maintain homeostasis. Acute stress studies have shown that morphological changes occur in microglia [213], but that they are not solely dependent on GCs [214]. In addition to changes in GC signaling [215], microglia have been found to respond to changes in neuronal activity via neuron-derived adenosine triphosphate signaling [216] and changes in norepinephrine concentration [217], both of which also change in multiple brain regions following stress [218, 219]. Other studies have implicated microglia in local cytokine production as the antibiotic minocycline reduced IL-1β levels in the hippocampus following stress exposure [220–222].

Contrasting acute stress, chronic stress exposure sees a decline in beneficial aspects. In response to chronic stress, higher activated microglia counts are observed (Fig. 1) [206, 223]. Further studies suppressing microglial activation found that this manipulation could ameliorate stress-induced memory deficits following CUS [224]. Furthermore, microglia engulf more dendritic material following CUS signifying a greater proportion of microglia are taking on a phagocytic state following stress [225]. The mechanisms driving increased phagocytosis are not fully understood, but it is proposed that this may be a response to physiological changes in neurons and an attempt to establish homeostatic brain activity [226].

In the healthy brain, neuron-microglia cross-talk is critical for maintaining the functional surveying state of microglia [227]. Notably, neurons release several soluble

factors such as adenosine triphosphate [228], colony-stimulating factor 1 (CSF1) [229], IL-34 [230], and fractalkine (CX_3CL1) [231] that bind to receptors expressed by microglia. Disruption of these communication pathways significantly changes stress effects. Pharmacological blockage of P2YR12, a microglial receptor that facilitates microglial process contact with neurons [232], results in limited dendritic spine loss on apical dendrites of pyramidal neurons within the PFC, implicating P2YR12 as a critical mediator of stress-induced morphological changes [233]. Another important signaling molecule involved in this cell-cell communication is CSF1. Exposure to CUS increased neuronal CSF1 levels in the PFC, and this was associated with microglial phagocytosis of neuronal elements and decreased dendritic spine density. Further studies showed that viral-mediated knockdown of CSF1 mitigated the synaptic and behavioral deficits following chronic stress (see Fig. 1) [62].

As previously discussed, chronic stress can result in enhanced myelopoiesis [135, 234] and redistributed immune cells throughout the periphery [154, 235]. Some studies suggest that these peripheral immune alterations promote monocyte trafficking to the brain, but this is observed primarily in the repeated social defeat model [236]. The presence of peripheral monocytes in stress-responsive brain regions such as the amygdala and hippocampus can promote anxiety-like and depressive-like behavioral responses with stress [237, 238]. Recently, a study using a social defeat model found that both circulating monocytes and brain-trafficking monocytes within stress-susceptible mice exhibited increased expression of a myeloid-cell-specific proteinase called matrix metalloproteinase 8 (*Mmp8*) [239]. More so, they found that *Mmp8* deletion attenuated neurophysiological and behavioral changes typically observed following chronic social defeat, further implicating monocytes in the neurobiology of stress. In contrast, other studies report that peripheral monocyte recruitment to the brain is not necessary for the behavioral alterations and microglial morphological changes that accompany social defeat exposure [226, 240]. These varied outcomes may be attributed to differences in stress models as well as experimental approaches.

Future Research Directions

Historically, microglia were largely regarded as a homogenous cell population in which each cell can shift between a "resting" and "activated" form [241]. However, the past few decades have seen remarkable advancements in microglia research including recent studies uncovering the heterogeneity of microglia across different brain regions [242–244] and how they take on specific forms in response to various diseases [245, 246]. This is relevant because stress is known to elicit brain region-specific changes in microglial density and morphology [247]. Further experiments using advanced approaches (i.e., scRNA-Seq) are needed to define region-specific microglial responses to stress and to understand their impact on associated neurobiology. In addition to region-specific microglia differences, neuronal circuit-specific stress-induced effects are another growing area of interest. Optogenetic studies stimulating connections between limbic structures have shown increased neuronal activity can reduce anxiolytic and depressive phenotypes induced by chronic stress (see Fig. 1) [248–250]. Continued studies investigating other connections and cell types (excitatory vs. inhibitory neurons) are required for further elucidation of stress-induced circuit-specific neurobiological changes.

Niches are restricted tissue microenvironments that maintain adult stem cells [251]. The heterogeneity of bone marrow and the study of bone marrow niches has been an emerging area of research for years [252]. Of particular interest to neuroimmunology, there has been increased attention given to the connection between the bone marrow of the skull and the meninges. Recently, with the use of tissue clearing and whole-body immunolabeling methods (vDISCO), a subset of short vascular connections between skull bone marrow and outer surfaces of the meninges were discovered and coined skull-meninges connections [253, 254]. Previously, it was thought that meningeal immune cells, such as myeloid cells and B cells, were supplied by systemic circulation, but recent developments have shown that these cells originate from the bone marrow of the skull [255, 256]. These intriguing results lead to the question, what role could skull bone marrow-derived myeloid cells have in the neurobiological changes associated with stress?

It is critical to point out that many studies highlighted in this review have been conducted in male rodents. There is substantial evidence that there are sex differences in the neurobiological effects of stress [257]. For instance, neuronal morphology of pyramidal neurons of the PFC after restraint stress or CUS has been shown to differ by sex [62, 258]. Microglia transcriptional changes following stress also appear to be sexually dimorphic [259, 260]. Sex-specific studies have ignited interest in investigating how sex hormones act as signaling molecules in the brain [261]. Estradiol has been of particular interest as it was

shown that estrogen receptors are widely distributed throughout the brain [262], have neuroprotective effects [263], and reduce stress effects when administered during stress regiments [258]. Also, studies investigating intrinsic connectivity networks subject to stress-induced changes [264] such as the default mode network [265], salience network [266], and executive control network have shown fluctuations in functional connectivity during the menstrual cycle [267], a reoccurring process in which the ovaries secrete varying estradiol levels. However, other estrogens, androgens, and progestogens, along with their active metabolites, remain understudied [268] particularly in neuroimmune and stress contexts.

Conclusion

The goal of this review was to provide historical context for research in the neurobiology of stress and psychoneuroimmunology. The studies discussed here have revealed how neuroimmune systems interface with the brain to affect behavior, but there is still much more to uncover about the function of these dynamic biological systems. Technological advancements in research will lead to new insights, but it is important to consider how our current work can be informed by or related to past studies. The history of stress is a collection of individual observations, some rigorously planned and some serendipitous, but all aid in understanding the physiological and behavioral changes caused by external pressures and internal perceptions. These experiences are a fundamental part of the human condition and validates our existence. In the words of Hans Selye, "The absence of stress is death."

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Conflict of Interest Statement

The authors have declared no conflict of interest exists.

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Author Contributions

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