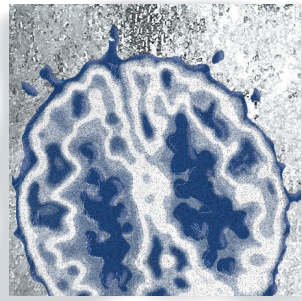


A multispecies approach for understanding neuroimmune mechanisms of stress

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Introduction

Stressful life experiences have the amazing ability to synchronize organism-wide physiological responses toward the common goal of surviving threat. In this way, the major stress-responsive systems are often regarded by evolutionary biologists as essential adaptive mechanisms that ultimately promote survival. However, as stress challenges become greater in magnitude or more protracted in length, the toll on the host organism can be quite severe, and the adaptive value of mobilizing physiological processes toward survival exacts a long-term cost. This essential framework for understanding the relationship between stress challenges and their impact on organism health was articulated by Hans Selye, who noted that nearly all stress challenges were followed by a “syndrome of being sick.”¹ Unbeknownst to Selye, this prescient view of the relationship between stressful experiences and their sickness-like outcomes, in today’s vernacular, implies that immune processes are probably essential mediators of the link between stress and adverse health outcomes. With this in mind, the present review takes the position that neuroimmune mechanisms of stress are highly conserved across species and serve as a likely mechanistic bridge between classic stress-responsive systems and stress-related pathologies (*Figure 1*).

The relationship between stress challenges and adverse health outcomes, particularly for the development of affective disorders, is now well established. The highly conserved neuroimmune mechanisms through which responses to stressors are transcribed into effects on males and females have recently garnered much attention from researchers and clinicians alike. The use of animal models, from mice to guinea pigs to primates, has greatly increased our understanding of these mechanisms on the molecular, cellular, and behavioral levels, and research in humans has identified particular brain regions and connections of interest, as well as associations between stress-induced inflammation and psychiatric disorders. This review brings together findings from multiple species in order to better understand how the mechanisms of the neuroimmune response to stress contribute to stress-related psychopathologies, such as major depressive disorder, schizophrenia, and bipolar disorder.

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Selected abbreviations and acronyms

CNS	<i>central nervous system</i>
CRP	<i>C-reactive protein</i>
GC	<i>glucocorticoid</i>
HPA	<i>hypothalamic-pituitary-adrenal</i>
IL	<i>interleukin</i>
LPS	<i>lipopolysaccharide</i>
MDD	<i>major depressive disorder</i>
PVN	<i>paraventricular nucleus</i>
TNF-α	<i>tumor necrosis factor α</i>

To support this position, we (i) provide a succinct overview of neuroimmune mechanisms of stress that have been largely established in preclinical (mouse and rat) models; (ii) extend these findings to other mammalian systems (guinea pigs and nonhuman primates); and (iii) translate these findings to the human

condition. The intent here is not to provide a comprehensive summary, but rather to succinctly link together commonalities across models/species that argue in favor of viewing neuroimmune consequences of stress as highly conserved across taxonomic orders. At the same time (and perhaps ironically), we argue that key features of the stress challenge (nature, intensity, and duration of threat), as well as individual subject characteristics (sex, age, stress history), will be critical for delineating individualized therapeutic approaches for the future. In doing so, we hope to provide guidance on significant gaps in our knowledge that remain to be filled and some possible pathways for the future. Although we focus largely on the link between stress and negative affective states, such as depression and anxiety, the same processes are probably involved in risk for other forms of psychopathology as well.

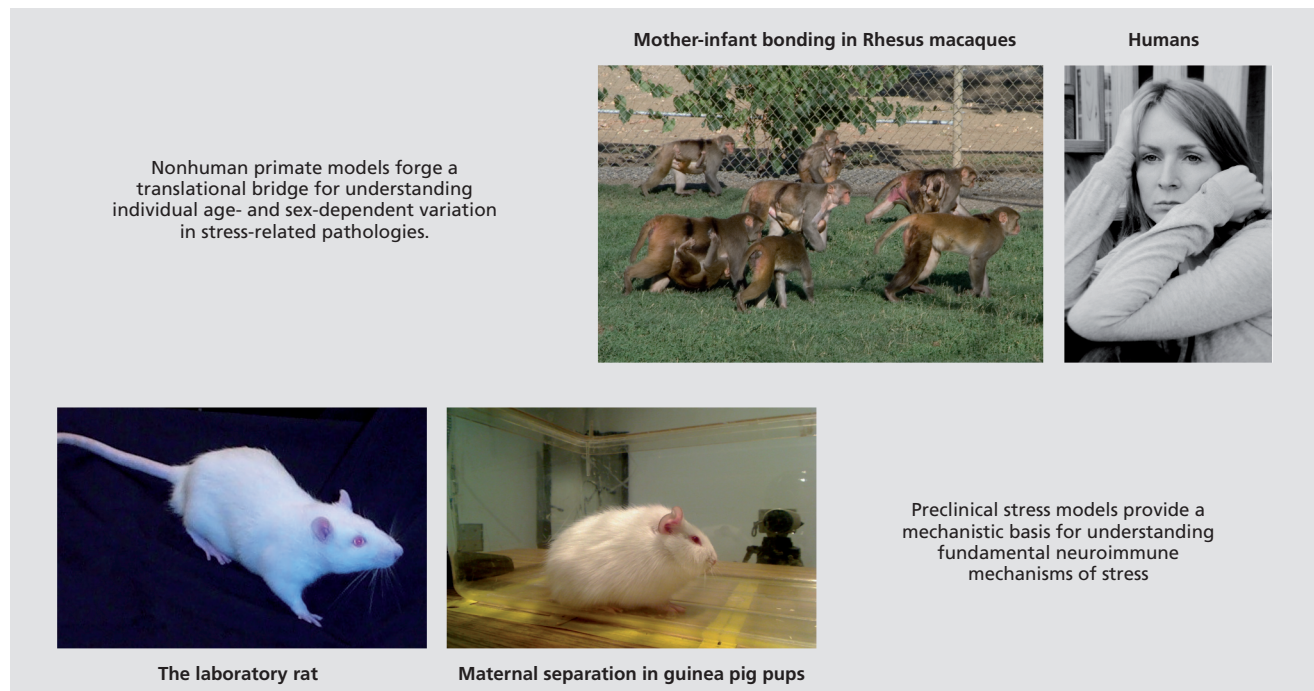


Figure 1. A multispecies approach toward understanding neuroimmune mechanisms of stress and their relation to human affective disorders. The neuroimmune consequences of stress are highly conserved across mammalian species, yet vary within species as a function of sex, age, and past history of stress. Mouse and rat models are commonly used to examine basic molecular and cellular components of the stress response. The use of guinea pigs is advantageous as they are born highly precocious and form a strong attachment to their mother, thereby creating a highly tractable model of maternal separation during early life. Findings from guinea pigs can be applied to generate hypotheses to test on nonhuman primates, such as rhesus macaques, which will then inform basic research and clinical applications in humans that can guide therapeutic approaches.

Rat photo courtesy of Dr Lisa M. Savage; guinea pig photo was contributed by Dr Michael B. Hennessy; photo showing troop of rhesus macaques was courtesy of the California National Primate Research Center; human photo courtesy of Anastacia Kudinova.

The first step in understanding neuroimmune mechanisms of stress and their eventual role in stress-related health outcomes is to define what is meant by “neuroimmune mechanisms.” Historically, most studies have focused on intercellular signaling factors, such as cytokines, chemokines, and the many species of prostaglandins, whose primary roles were initially defined within an immunologically relevant context. Demonstration that such intercellular mediators are often invoked by stress challenges in which there is no apparent tissue damage or other immunological insult suggests a natural role for these agents in mediating stress outcomes. However, the identification and interpretation of such findings can be quite difficult because there are literally dozens of inflammatory signaling factors that can be simultaneously regulated; cytokines often have redundant biological action with one another; and nearly all cytokines have pleiotropic functions. Even more troublesome is the fact that actions of cytokines can manifest as generally pro- or anti-inflammatory, depending upon the presence of other signaling molecules and the context in which they are induced.

In addition to these conceptual issues surrounding the identification and interpretation of cytokine action, there are also technical considerations surrounding the assessments of cytokines and other immune mediators. Because immune-related factors are expressed at appreciably low quantities in the normal central nervous system (CNS), the techniques to detect and measure such cytokines, particularly in early studies, have often been inadequate to yield precise results. For instance, many studies have utilized gross tissue dissections (or micropunches) that aggregate cytokine measures over large anatomical areas and across cell types within the dissected tissue, which can significantly influence outcomes and interpretation.² A second major technical consideration lies in the use of quantification procedures that allow for signal amplification (reverse transcription polymerase chain reaction) versus those that do not (in situ hybridization), and the more general juxtaposition of studies that measure protein versus messenger RNA (mRNA). The availability of well-validated antibodies and the use of appropriate immunohistochemical controls for target specificity and cell type have also been a historical problem.³ Finally, deploying standard neuroscientific approaches (canulation, lesions, etc) for manipulation of inflammatory signaling in the CNS can significantly alter sensitivity

to later stress challenges.⁴ Thus, one must carefully consider the technical approach employed by studies as a key constraint in interpreting experimental outcomes.⁵⁻⁷

With that said, several inflammatory mediators have emerged as highly stress-responsive, and their physiological impact has been delineated clearly. For instance, numerous studies have indicated that interleukin (IL)-1 β is rapidly increased in key limbic structures (paraventricular nucleus [PVN]; amygdala) in response to stress challenges that involve application of an aversive/noxious stimulus such as footshock,⁷⁻¹⁰ but not in response to social stress challenges.¹¹ In contrast, social stressors appear to increase release of another proinflammatory cytokine, IL-6, in both plasma and brain of mice, thereby contributing to stress phenotypes.^{12,13} Importantly, recent evidence suggests that early exposure to maternal separation in male rats may change cytokine reactivity to later social stress challenges incurred during adulthood.¹⁴ Moving beyond some of the classic cytokines (such as IL-1 β , IL-6, tumor necrosis factor α [TNF- α]), recent evidence suggests that chemokines are also dynamically altered by stress challenges.^{8,15,16} As a separate class of immune-related molecules, these stress-induced chemokines probably play a key role in structural changes to the cytoskeleton of microglia that allows for the motility and retraction of processes,^{17,18} in recruitment of other intrinsic microglia to the site of release,^{19,20} and in potentially inducing passage of monocytes across the blood-brain barrier.^{21,22} Indeed, genetic ablation of the chemokine CX3CL1 (fractalkine) was recently shown to prevent microglial activation associated with chronic unpredictable stress.²³ In addition, prostaglandins have emerged as rapid, stress-sensitive inflammatory mediators, particularly within the cortex.²⁴ Given the role that prostaglandins play as final common mediators of the febrile response, prostaglandins are also likely mediators of stress-induced fever responses.²⁵ Thus, a multitude of inflammatory signaling families are mobilized by stressful experiences and significantly impact CNS function.

A growing number of studies have also examined cellular manifestations of neuroinflammation, with microglia emerging as highly reactive to stress challenges. Early studies examining microglial activation established that administration of minocycline, a putative microglial inhibitor, blocked the induction of central, but not peripheral, IL-1 β by footshock.^{8,26} Other studies have shown that chronic stress exposure drives prolifer-

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ation of microglia²⁷ and increases both the density and activation state of microglia within certain brain structures.^{23,28-30} Stress challenges also alter the expression of receptors expressed on the cell surface of microglia that are both indicative of microglial activation state and positively coupled to cytokine expression within microglia.^{8,31} Indeed, dynamic alterations in cell surface receptors on microglia probably accounts, at least in part, for certain priming/sensitization effects incurred by stress, including more rapid cytokine responses produced by later injection of lipopolysaccharide (LPS).^{32,33} Together, these findings provide multiple avenues by which stress challenges impact microglia and strongly support the notion that microglial (re)activity may be a key culprit in mediating stress-dependent changes in behavior,³⁴ cognition,³⁵⁻³⁷ and potentially multiple forms of psychopathology.^{38,39}

The importance of inflammatory phenotype to behavioral and mood-related changes incurred by stress has been strengthened in recent years through the use of adoptive transfer studies. These clever studies show that repeated exposure to various forms of repeated social stress in mice increases microglial activation and expression/release of cytokines. Intriguingly, when circulating monocytes are then extracted from previously stressed mice and transferred to other mice in which the existing monocytes/lymphocytes have been depleted, the recipient mice display behavioral and mood tendencies that reflect those of the original stressed host.⁴⁰⁻⁴² These findings, combined with recent evidence showing that circulating monocytes may transit into the CNS as a result of stressor exposure and actively influence mood state,^{15,43} add a new dimension to our understanding of bidirectional communication between the brain and the peripheral immune system.⁴⁴ Though this provocative area of research is still in its infancy, the emerging body of evidence provides, for the first time, causal evidence for the notion that non-neuronal cells (microglia) may be responsible for encoding stress-dependent changes in mood regulation, particularly for negative affective states like depression and anxiety.^{45,46}

A key issue that must be considered in understanding the relation between stress challenges and their neuroimmune consequences is *timing*. In laboratory models, acute stress challenges or the individual bouts of daily, intermittent chronic stress procedures are typically elaborated across a 30-min to 3-hour window of stress exposure (*Figure 2*). The central questions requir-

ing consideration here are (i) How rapidly are neuroimmune signaling agents induced? (ii) How long do such changes persist? (iii) Are there downstream neuroimmune effects that cascade or coalesce into subsequent neuroimmune alterations? and (iv) What are the functional outcomes that can be tied to individual components of such neuroimmune cascades? Although the discussion above did not address these issues by indicating the time point at which individual changes were observed, recent studies examining the time course for neuroimmune responses provide some guidance. For instance, induction of IL-1 β gene expression is prevalent and significant within 30 min of stress *onset*,^{6,7} with IL-1 β protein responses peaking shortly thereafter (60 to 120 minutes after stress onset).⁴⁷ In contrast, most studies examining microglial morphology, proliferation, or activation state tend to show changes that are prevalent 24 hours or more after stress *termination*,^{28,29} by which point many cytokine changes have largely re-

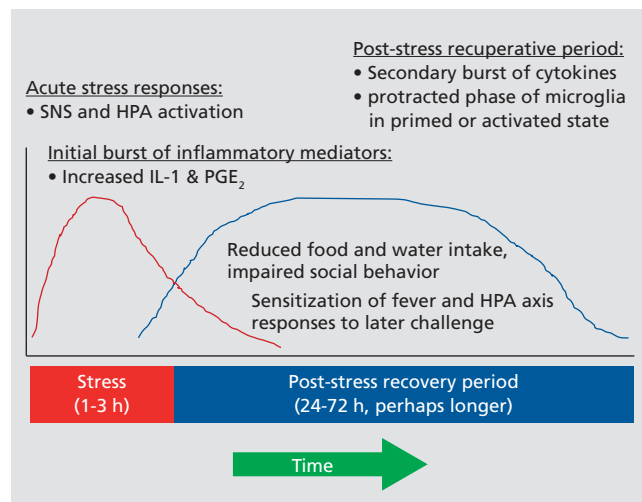


Figure 2. Stress-related neuroinflammation mediates the post-stress recuperative period. Acute stress induces activation of the sympathetic nervous system and HPA axis, leading to release of inflammatory factors, such as cytokines (eg, IL-1), chemokines (eg, CCL2/MCP1), and prostaglandins (eg, PGE₂). These factors regulate various features of the post-stress recuperative period, in which the subject displays reduced food and water intake, impaired social behavior, and often sickness-like responses. This constellation of behavioral changes probably represents a recuperative motivational state that promotes recovery after intensely stressful experiences. CCL2/MCP1, chemokine (C-C motif) ligand 2, also referred to as monocyte chemoattractant protein 1; HPA, hypothalamic-pituitary-adrenal; IL, interleukin; PGE₂, prostaglandin; SNS, sympathetic nervous system

solved. Though perhaps correlational at this stage, one interpretation of the timing of these events is that the expression and release of intercellular mediators (cytokines, chemokines, prostaglandins) have a nearly immediate impact upon behavioral changes observed in the post-stress recuperative period, while at the same time eliciting parallel changes in other aspects of neuroimmune function that persist for days to weeks after cessation of stress. Thus, it will be critical for future studies to conceptually discriminate between those neuroimmune changes that represent acute, activation responses to an individual bout of stress, versus those neuroimmune changes that reflect the aggregate influence of a repeated history of stress across a more protracted period of time.

Mechanisms underlying stress-related neuroinflammation

The multitude of inflammatory signaling pathways that appear to be activated by stress challenges raises questions regarding the mechanisms that control such neuroimmune changes. Here, we suggest that multiple upstream signaling pathways converge upon regulatory elements associated with neuroimmune signaling, thereby propagating various features of the neuroimmune response to stress. For ease of description, we will describe these pathways in three functional clusters (Figure 3), with full recognition that these pathways are not independent of one another. The first of these mechanisms falls into the general category of *rapid neural signals*. For instance, norepinephrine release during stress-associated activation of the sympathetic nervous system has long been regarded as a primary driver of neuroimmune consequences of stress.^{6,26} A wide range of pharmacological studies lend support to this notion, showing that administration of β -adrenergic blockers (eg, propranolol) block the induction of IL-1 β incurred by stress, whereas β -adrenergic agonists (eg, isoproterenol) potentially induce IL-1 β expression.^{8,26,48} Consistent with this, previous treatment with desipramine (a norepinephrine-reuptake inhibitor) potentiated both basal and stress-induced IL-1 β expression.²⁶ Gross neurotoxic lesions of norepinephrine-containing cells via intracerebroventricular injection of the selective neurotoxin N-(2-chloroethyl)-N-ethyl-2 bromobenzylamine (DSP-4) blocked the induction of IL-1 β in the hippocampus,⁴⁸ whereas more focal lesions of the ven-

tral noradrenergic bundle produced modest effects on IL-1 induction by stress in the PVN.⁶ Together, these studies underscore the importance of norepinephrine signaling as a key driver of neuroimmune consequences of stress. However, other studies have clearly tied microglial proliferative responses incurred by chronic stress to glutamate signaling, since chronic administration of MK801 effectively blocked this proliferative response,²⁷ and N-Methyl-D-aspartate (NMDA)-receptor activation is positively coupled to inflammatory signaling pathways.^{49,50} Interestingly, considering that adenosine triphosphate (ATP) is co-packaged and released with many classic neurotransmitters (including norepinephrine, in particular), other groups have recently posited purinergic signaling as a putative mechanism controlling functional release of IL-1 β (and potentially other neuroimmune factors) in response to stress.^{2,51,52}

Another emerging class of neuroimmune intermediaries falls into the category of what we describe as *danger, damage, and disease signals* (Figure 3).⁵³ The basic premise is that our innate immune defense network is constructed to respond to general molecular motifs associated with pathogens or self-injury. DAMPs—damage-associated molecular patterns—are host-derived molecules that are released in response to tissue trauma or other insults and are thus capable of activating inflammatory signaling pathways. A variety of studies have convincingly demonstrated several families of DAMPs that are activated by exposure to intense stress challenges, including heat shock proteins (HSP72, in particular)⁵⁴ and high-mobility group box 1 (HMGB1).^{55,56} When released, these DAMPs interact with cognate receptors that are positively coupled to inflammatory signaling pathways. This family of receptors is often referred to as pathogen recognition receptors (PRRs) because they recognize and bind to general molecular motifs associated with classes of bacteria and viruses, as well as to certain DAMPs that may be activated by stress and/or damage. Yet another intriguing twist is the recent notion that bacteria from the gut or other areas of the microbiome may be stress sensitive, and perhaps even mobile in response to stress challenges, thereby incurring a mild form of endogenous infection.⁵⁷⁻⁵⁹ Thus, the DAMP \rightarrow PRR pathways have emerged as important alternative pathways by which neuroimmune consequences of stress are primed and/or activated.⁶⁰

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The propagation of neuroimmune signaling cascades in response to stress is also *constrained* by other features of physiology. Perhaps the most logical of these counter-regulatory elements is the release of glucocorticoid (GC) hormone (corticosterone in rat and mouse; cortisol in guinea pigs and primates) as a result of hypothalamic-pituitary-adrenal-axis (HPA) activation that accompanies stress exposure. The anti-inflammatory action of GCs has been established for decades, with great

progress being made in recent years in the *cis*- and *trans*-regulatory elements that give rise to anti-inflammatory effects of GCs.^{61,62} Within stressful contexts, this was particularly evident in early studies where induction of central IL-1 β was massively potentiated in adrenalectomized subjects, and normalized by replacement of corticosterone.^{10,47} Similar effects have been observed after pretreatment with metyrapone (a GC synthesis inhibitor).^{8,26} However, there appear to be certain instances in

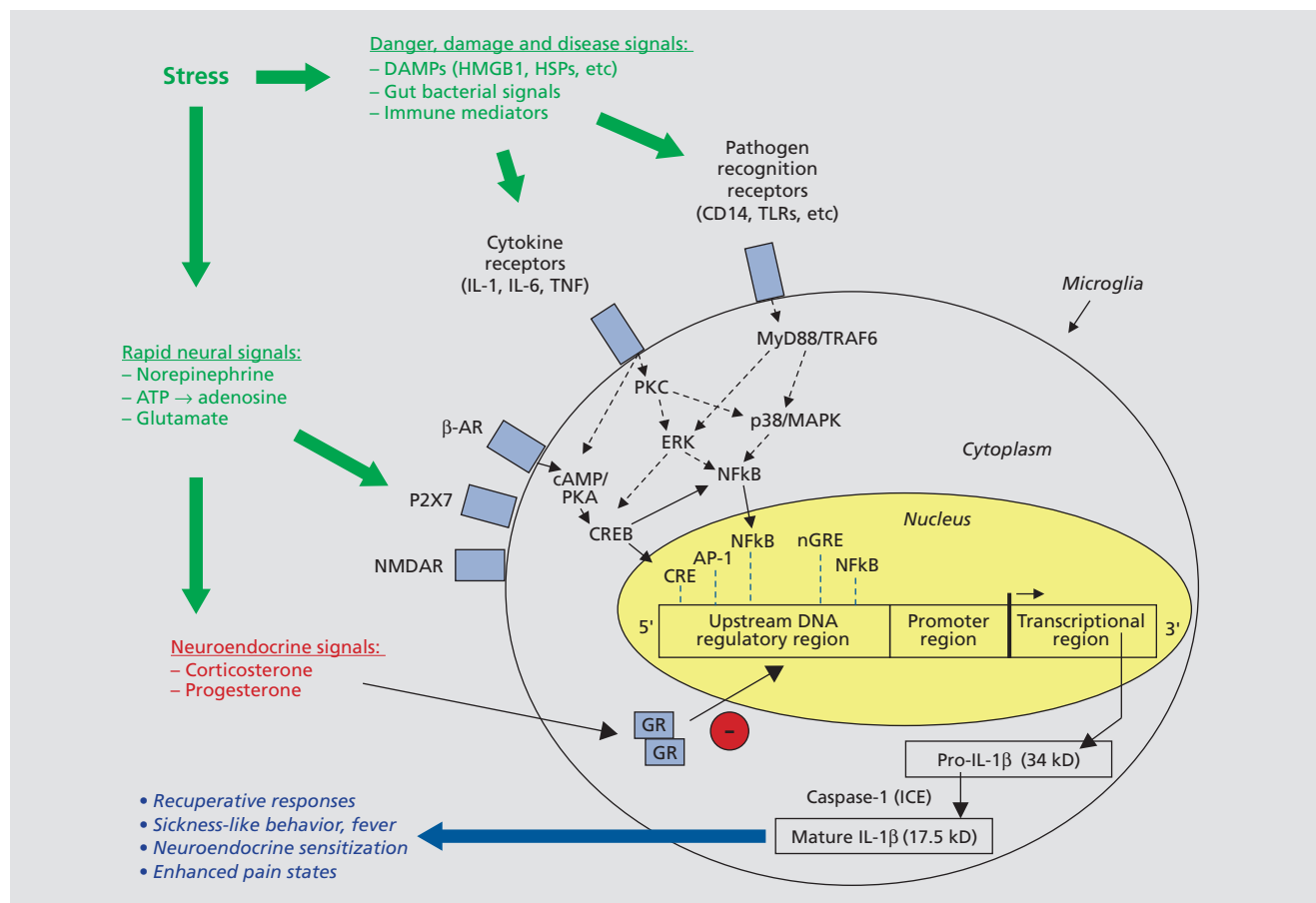


Figure 3. Signaling molecules involved in regulating stress-related neuroinflammation. Neuroimmune signaling molecules that control inflammatory response can be categorized into three types, as follows: (i) host-derived danger, damage, and disease signals—including cytokines, chemokines, and damage-associated molecular patterns (DAMPs)—that acutely activate inflammatory signaling pathways; (ii) rapid neural signals, such as norepinephrine and glutamate, that rapidly drive the stress response and cytokine production throughout the body; and (iii) neuroendocrine signals, particularly corticosteroids and progesterone, which may serve to constrain the inflammatory process and dampen production of inflammatory factors. AP-1, activator protein 1; ATP, adenosine triphosphate; AR, adrenergic receptor; cAMP, cyclic adenosine monophosphate; CRE, cAMP-response element; CREB, cAMP-response-element binding protein; DAMPs, damage-associated molecular patterns; ERK, extracellular-signal-regulated kinase; GR, glucocorticoid receptor; HMGB1, high-mobility group box 1; HSPs, heat shock proteins; ICE, interleukin-1-converting enzyme; IL, interleukin; MAPK, mitogen-activated protein kinase; MyD88, myeloid differentiation primary response gene 88; NF κ B, nuclear factor κ B; nGRE, negative glucocorticoid response element; NMDAR, N-methyl-d-aspartate receptor; PKA, protein kinase A; PKC, protein kinase C; TNF, tumor necrosis factor; TLR, Toll-like receptor; TRAF6, TNF receptor-associated factor 6

which GCs prime or modestly stimulate inflammation, a notion which is now challenging some of the central dogma on the relation between GC hormone signaling and inflammation.⁶³ These latter, proinflammatory-like effects of GCs probably represent a small proportion of the overall GC effects on inflammation and relate to very specific parameters of low GC dose, the timing of GC hormone exposure, and the specific tissue in which the GCs act.⁶⁴⁻⁶⁶ Gene expression profiling studies predict such effects,^{53,67} and so it is quite interesting to see these effects bearing out on functional responsiveness within the neuroimmune system. Furthermore, a recent study found that microglial activation was more profound after several weeks of repeated restraint, but not after an equivalent exposure to chronic variable stress.²⁹ Although the reason for this difference has yet to be determined, the authors propose that HPA-axis habituation, and thus the lack of circulating GC hormone that accompanies repeated restraint, led to a disinhibition of stress-dependent microglial activation. Additional studies showed that pharmacological activation of the HPA axis (in the absence of an overt stress challenge) via corticotropin-releasing hormone or corticotropin injection led to an expected inhibition of cytokine expression in the PVN, though paradoxically, both peptides stimulated inflammatory signaling at the level of the adrenal gland.⁷ Yet another added complexity is that GCs are not the only hormone system engaged by stress exposure. Recent studies demonstrated that progesterone is also rapidly released in response to stress, even in male rats. This makes sense as progesterone is a precursor molecule in the biosynthesis of corticosterone, yet the possibility that progesterone may contribute to the anti-inflammatory influence of GCs has not been systematically tested.⁶⁸

One major area of neglect in the literature has been the elaboration of *sex differences* in neuroimmune responses to stress. In a recent set of studies from our lab, we examined fluctuations in the IL-1 β response to stress as a function of estrous stage in female rats.⁶⁹ These studies reported relatively uniform IL-1 β induction at all phases of the cycle except during metestrus—where basal IL-1 β was moderately increased, and the IL-1 β response to stress appeared to be blunted in the PVN. However, this effect requires further study to generalize the effects from mRNA to protein, to expand the analysis from the PVN to other stress-sensitive sites, to incorporate additional neuroimmune measures, and to

replicate what was originally a slightly underpowered effect. Nevertheless, subsequent studies demonstrated that stress-induced IL-1 β was potentiated in ovariectomized rats and restored by estradiol-replacement injections. However, because endogenous progesterone evinced a stress-induced surge, we cannot at this time attribute the “rescue” effect of estradiol replacement exclusively to estradiol (versus an estradiol plus progesterone effect). What we do know, however, is that progesterone replacement alone did not recapitulate the effect of estrogen replacement. Nevertheless, few studies, if any, have examined how sex-specific gonadal steroids differentially affect sex differences in neuroimmune responses to stress in rodents. Thus, future studies need to give serious consideration to potential additive, cooperative, and synergistic effects of steroid hormones on stress-dependent changes in neuroimmune function.⁵³

Social separation and inflammation: guinea pig and monkey models

Although the vast majority of studies on stress and inflammation have focused on rats and mice (as indicated in the above discussion), investigators have sometimes turned to alternative rodent species.⁷⁰⁻⁷² Guinea pigs in particular offer a number of advantages, especially in developmental studies. Unlike rats and mice, guinea pigs are born in an advanced state of development. Brain regions are well defined, and the skull is calcified even in the first few days, which facilitates procedures such as implanting indwelling cannula and immunohistochemistry. Thermoregulation matures rapidly,⁷³ so LPS- or stress-induced fever can be investigated early in preweaning pups. But for studies of stress-induced inflammatory responses during infancy, perhaps the greatest advantage stems indirectly from the fact that the pups are precocial. Guinea pigs are capable of coordinated behavior, including locomotion and ingestion, from shortly after birth.⁷⁴ Maternal behavior is extremely passive. Licking of the pups, the primary active maternal behavior, is infrequent, particularly after about a week of age.⁷⁵ There is no retrieval, no nest, and mothers simply accommodate nursing attempts initiated by the pups.⁷⁶ As a result, mother-young proximity is maintained almost exclusively by the strong attraction or attachment that pups display for the mother. Indeed, pups exhibit evidence of the classic markers of attach-

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ment commonly used in primate studies—namely, approach, recognition, and preference for the attachment object; use of the attachment object as a secure base for exploration; and distressful responses to separation.⁷⁷⁻⁷⁹ Maternal separation in guinea pigs thus affords a compelling translational model for the effects of attachment disruption, a class of early stressors frequently linked to later psychopathology in humans as well as altered inflammatory activity.^{38,80,81}

There are many similarities in the responses to maternal separation shown by young guinea pigs and infant monkeys.⁸² These include, for instance, increased HPA and sympathetic activity^{83,84} and central catecholamine turnover associated with stress.^{85,86} As is seen in some species of macaques,⁸⁷ as well as in human infants,⁸⁸ guinea pig pups also display a two-stage, active/passive behavioral response to separation. When placed alone in a novel cage, pups initially show “protest” by vocalizing in an apparent attempt to re-establish contact with the mother. But after about an hour of separation, the pups typically quiet and adopt a characteristic crouched stance, with closed eyes, extensive piloerection, and apparent disinterest in their surroundings (*Figure 1*).⁸⁹ Neither the active nor passive stages are observed if the mother is placed in the novel cage with the pup,⁹⁰ establishing that the mother’s absence, and not just the novelty of the environment, is responsible for these responses. The passive, second stage of separation in guinea pig infants is reminiscent of the “despair” shown by monkeys separated for much longer periods⁹¹ and even the “anaclitic depression” that Spitz (1946) described in institutionalized children.

Although the nature of the passive stage of separated guinea pig pups can suggest depression to a comparative psychologist, it may just as readily suggest cytokine-induced sickness behavior to the psychoneuroimmunologist. Each of the components of the response—crouch, eye-close, piloerection—is characteristic of sick animals.⁹² Moreover, direct stimulation of sickness with LPS results in the same behavioral constellation of these three behaviors.⁹⁰ It appears then that the stressor of separation in a novel environment initiates an inflammatory reaction that mediates the behavioral response. This claim is bolstered by findings that the separation procedure elicits a transitory fever⁹³ and increased expression of the proinflammatory cytokine TNF- in spleen,⁹⁴ two physiological indicators of a sickness response. Behaviors of the second stage of

separation can also be reduced by a variety of anti-inflammatory agents, including α -melanocyte-stimulating hormone (α -MSH),⁹⁵ indomethacin,⁹⁶ IL-10,⁹⁷ and naproxen.⁹⁸ Although other systems are also probably involved, it is clear that inflammatory mechanisms play a fundamental role in the depressive-like response of separated guinea pig pups. In the adult human literature, there is now overwhelming evidence for involvement of inflammation in depressive illness (as described below).⁹⁹ The guinea pig results suggest that the particular form of depressive response shown by separated nonhuman—and perhaps human—primate infants may also be mediated, at least in part, by inflammatory factors.

Most current research on attachment disruption and depression in humans focuses not on immediate effects, but rather on long-term vulnerability for developing depression engendered by early abuse, neglect, or prolonged separation. Whereas increased risk for later depressive illness has long been *suspected* for infants exposed to such forms of maltreatment,¹⁰⁰ recent research has solidified this link and begun to provide glimpses of potential neurobiological mechanisms. The basic premise common to most hypotheses is one of sensitization. That is, the early stress of attachment disruption is seen as sensitizing underlying stress-responsive machinery so that, in later life, exposure to stressors with which other individuals would be able to effectively cope elicit disproportional, protracted, and inadequately regulated stress responses that lead to, or constitute the underlying basis of, the depressive episode.¹⁰¹ These “diathesis-stress” or “two-hit” models have most often emphasized effects on elements of the HPA axis and its control, including increases in central corticotropin-releasing-factor secretion, amygdala activity, and GC resistance, as well as a reduction in HPA inhibition by the frontal cortex.^{80,101-103}

However, recently, there also has been a proliferation of findings implicating inflammatory mechanisms in the sensitization process. Attachment disruption and other forms of early stress have repeatedly been found to be associated with increased markers of inflammation at later ages.¹⁰⁴⁻¹⁰⁹ From an evolutionary perspective, the increased inflammation may represent a remnant of an ontogenetic adaptation originating from a time when persistent early-life stress was predictive of a hazardous adult environment, in which injury was common and a robust innate immune system was adap-

tive.¹¹⁰ The process by which early stress enhances later inflammation remains unclear but may involve sensitization of resident microglia or increased transport of peripheral monocytes to the CNS,^{111,112} resulting in heightened central release of inflammatory mediators. The augmentation of inflammatory processes, in turn, may be driven by activation of, and alterations in, other stress-responsive systems, such as increased resistance to the suppressive action of GCs and elevated sympathetic activity.^{38,107,113}

Results of guinea pig studies implicate inflammatory factors in long-term effects of early stress. Repeated separation increases, ie, sensitizes, both the depressive-like behavior and febrile response to later separations during both the preweaning period and beyond. Moreover, administration of the cyclooxygenase (COX)-inhibitor naproxen before the initial separation suppressed the sensitization response not only to the initial separation experience but also to separations that followed 1 and 10 days later.⁹⁸ The sensitization that occurs appears to be related to some broader, depressive-like state rather than just the separation response, as previously separated guinea pigs also showed more immobility in the forced swim test, a measure and paradigm that is selectively sensitive to antidepressant medications.

In these studies, as is the case in the field more generally, sex differences have yet to be a major focal point. Although males and females have typically both been included in the guinea pig work, it has been in numbers too small to sufficiently power examination of male-female differences. However, as rodent models for the role of inflammation in stress-related disease are now becoming established, it is imperative that male-female differences be taken into account. This is particularly important for disorders in which sex differences are profound, such as major depression, for which women are about twice as likely as males to be afflicted.

Social separation in adult macaques

The above results argue that the guinea pig model has strong internal validity in that there is good evidence that attachment disruption in the form of maternal separation results in depressive-like behavior that sensitizes with repeated separation. The evidence also indicates that the sensitization involves inflammatory processes and reflects changes in an underlying state that is manifested in more than one depressive-like response. The

external validity, ie, the generality of the results to humans, would, however, be bolstered if we could demonstrate that a similar experimental procedure produced similar results in a primate. Indeed, the guinea pig work was always intended as a complement to primate research; that is, as a way of doing the investigative work necessary to ultimately generate hypotheses that might then be tested in primate models. The challenge has been how this might be accomplished without proposing to repeat the prolonged separation of monkey infants from their mothers that was common in experiments of the 1950s and 1960s.

A possible solution arose from observations of the Behavioral Management Unit and others at the California National Primate Research Center. It was noted that when adult monkeys were brought from large outdoor social groups (*Figure 1*) to restricted indoor housing, as is commonplace for the beginning of experiments or veterinary care, a small proportion exhibited a hunched posture with apparent disinterest in their surroundings, a response that both is widely regarded as indicating a depressive-like reaction in macaques¹¹⁴ and which mimics the reaction observed in separated monkey infants. Furthermore, when recordings of adult male monkeys introduced to the restricted indoor housing with no human observer in the room were analyzed, an even larger percentage of animals were found to exhibit the depressive-like hunched posture.¹¹⁵ These findings suggest that presence of a human may evoke a defensive reaction incompatible with the depressive-like response. These findings are compatible with interpretation of these depressive-like consequences as a manifestation of sickness, since expression of sickness behaviors are easily perturbed in the face of threat.¹¹⁶ From a modeling standpoint, however, the observations suggested that the relatively simple procedure of transferring adult monkeys from outdoor social groups to indoor housing may provide a means of evaluating the general relevance of the guinea pig results for nonhuman primates.

Therefore a new model was developed in which adult male rhesus macaques were brought from half-acre outdoor social groups to standard indoor housing, either alone or together with an affiliative juvenile partner for 8 days on two occasions at an approximate 2-week interval. Behavior was filmed without a human observer present and blood samples were taken for cytokine analysis at the end of each 8-day period of in-

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door housing, as well as when the males were residing in the outdoor field cages. During the first separation, all monkeys of both groups exhibited the hunched posture, with an average of about a third of all observation time spent in this posture.¹¹⁷ During the second separation, time spent in the hunched posture increased (ie, sensitized), but only for those males housed alone. The increase in time spent in the hunched posture was accompanied by a decline in activity and environmental exploration.

There also were several effects on cytokine measures. The monkeys housed alone showed a relative decline from the first to the second period of indoor housing in LPS-induced expression of the anti-inflammatory cytokine IL-10, whereas those monkeys housed with a partner showed a relative increase. Furthermore, regardless of whether monkeys were alone or with a partner, indoor housing reduced sensitivity of the pro-inflammatory cytokines IL-1 and TNF- to the suppressive action of GCs. It should be noted that both of these measures—response to LPS stimulation and GC resistance—were chosen because they appear responsive to early-life stress in humans.¹⁰⁷ Finally, evidence for a coupling of the behavioral and cytokine findings was also observed. For monkeys tested alone, a large and significant positive correlation was observed between the number of seconds spent in the hunched posture during each period indoors and circulating levels of each of the three cytokines measured. Although many particulars of the experimental design and measures in the guinea pig and monkey studies differed, the broad similarity of results suggests some cross-species commonality or conservation of basic relations between social separation, inflammatory activity, and depressive-like behavior and its sensitization. The findings also suggest relatively simple rodent and monkey models that might be used to continue to disentangle the way in which early-life stress and inflammation contribute to depressive illness and other negative affective states.

Neuroimmune response to stress: human literature

The key question, of course, is how well these animal models translate to humans and help us better understand the human stress response and risk for psychopathology. Psychosocial stress is a well-established risk factor for the development of various forms of psycho-

pathology in humans, including major depressive disorder (MDD), posttraumatic stress disorder (PTSD), and other anxiety disorders.¹¹⁸⁻¹²¹ Similar to findings from animal models of stress, evidence from human studies shows that exposure to stressors provokes neurochemical changes, including changes in levels of inflammation, that are frequently associated with psychopathology, and which may help to explain the mechanisms by which stress increases risk for psychiatric disorders, including MDD.^{38,122} Neuroimmune effects of exposure to stressful events can persist beyond the immediate impact and potentiate an individual's response to future stressors, thus increasing risk for future psychopathology.^{105,107,123} Indeed, among individuals with MDD, those who experienced childhood adversity had higher circulating levels of C-reactive protein (CRP) than individuals with no history of childhood trauma.^{124,125} Additionally, adults who experienced childhood adversity exhibited higher levels of circulating IL-6 levels in response to an acute stressor.¹⁰⁵ Finally, there is preliminary evidence that a haplotype in *IL-33* moderated the link between women's history of childhood abuse and their risk for depression in adulthood.¹²⁶

Across a variety of stressors, ranging from low socioeconomic status to traumatic events, mammalian immune cells show an immediate conserved transcriptional response to adversity, which involves increased expression of inflammatory genes and decreases in the genes underlying antiviral responses.^{113,127-131} Interestingly the inflammatory component of the leukocyte conserved transcriptional response to adversity may be driven by stress-induced upregulation of myelopoiesis and could contribute to development of negative health outcomes associated with adverse social conditions, including psychiatric disorders.¹³² Overall, one of the pathways for the effects of exposure to stressors on psychopathology risk seems to be an increase in immediate and long-term expression of immune-related genes, outcomes that appear to recapitulate effects observed in preclinical (animal) models. Immune-related transcripts involved in the cellular stress response have been shown to be upregulated in the prefrontal cortex (PFC) of individuals with schizophrenia, indicating that these genes may play an important role in chronic psychopathology. Importantly, these observed transcriptome changes were not a result of acute immune system activation, as there were no differences in markers of acute inflammation or responses to infections between

individuals with schizophrenia and controls.¹³³ Similarly, in the hippocampus, general upregulation of inflammatory transcripts was found in patients with MDD, bipolar disorder, and schizophrenia, though the authors reported no overlap in specific genes across disorders.¹³⁴ This suggests that there are common immune-related gene changes in psychiatric disorders, but that there are also changes in expression that are differentially regulated between diseases. For example, circulating cytokines and upregulation of immune-related genes have been found to occur in patients undergoing a first episode of psychosis, whereas those with comorbid depression displayed a unique expression profile, suggesting separable transcriptional phenotypes.¹³⁵ Additionally, increased mRNA levels of chemokine (C-C motif) ligand 24 (CCL24) were found in circulating leukocytes among participants with MDD compared with individuals with bipolar personality disorder and healthy controls. In contrast, C-C chemokine receptor type 6 (CCR6) was expressed consistently less among MDD patients than in controls.¹³⁶ These immune targets may represent easily testable biomarkers of disease. Another example can be found in common variants in long-range enhancer elements that modulate transcriptional response to activation of GC receptors in human blood cells, thereby increasing the risk for later psychopathology, including MDD and schizophrenia.¹³⁷ Moreover, those functional genetic variants were associated with overgeneralized amygdala reactivity, suggesting that individual differences in the leukocyte's immediate transcriptional reactivity to stress may influence an individual's neurophysiological response to stress.

Epigenetic alterations in genes related to immune function are one of the plausible mechanisms underlying the lasting neuroimmune effects of stress exposure and increased risk for psychopathology. One of the first epigenome-wide association studies (EWAS) that examined DNA methylation among participants with a history of MDD identified tryptophan metabolism-related genes as one of the top three functional clusters in individuals with no history of MDD,¹³⁸ one of which was a cytokine-induced reduction in tryptophan, the primary serotonin precursor often implicated in MDD.¹³⁹ There is also evidence that methylation levels of the *IL-6* and *CRP* genes are inversely related to circulating levels of IL-6 and CRP among individuals with a history of MDD.¹³⁸ Similarly, immune-related genes were shown to be over-represented among unmethylated

genes among individuals with PTSD.^{138,140} Furthermore, hypomethylation of immune-related genes among PTSD-affected individuals was linked to increased peripheral levels of inflammatory cytokines, which were, in turn, related to history of childhood abuse and life stress.¹⁴¹ Overall, these findings suggest that exposure to stressors, perhaps particularly early-life stress, could result in immune-associated epigenetic changes that increase an individual's susceptibility to psychiatric disorders.

Complementing these findings, researchers have recently begun exploring neural mechanisms underlying immune activation after stress exposure in humans via structural and functional imaging. For example, a functional magnetic resonance imaging study that examined changes in mood and neural activity after an in vivo immune challenge found that immune-induced mood decline was associated with increased activity in the subgenual anterior cingulate cortex (sACC) during emotional face processing.¹⁴² Inflammation-induced mood deterioration was also associated with decreased functional connectivity of the sACC with the amygdala, medial PFC, nucleus accumbens, and superior temporal sulcus. Additionally, exposure to an acute social stressor has been associated with increased circulating levels of IL-6 and TNF- α , along with increased activity in the dorsal ACC (dACC) during a social rejection task.¹⁴³ These findings suggest that stress-induced effects on inflammation may increase activity in brain regions associated with emotion processing, while decreasing connectivity with regions involved in emotion regulation. This increased sensitivity to social stressors and decreased emotion regulation may, in turn, increase the risk for various psychiatric disorders, including MDD.¹⁴⁴

There is growing evidence that inflammation may also impact corticostriatal reward circuitry, which underlies symptoms of anhedonia that are common in various psychiatric disorders.¹⁴⁵ Specifically, there is evidence that increased circulating levels of CRP, a common inflammatory marker, were associated with decreased connectivity between ventral striatum and ventromedial PFC and decreased dorsal striatal to ventromedial PFC connectivity among participants with MDD.¹⁴⁶ Notably, the association between the differences in connectivity and symptoms of anhedonia and motor slowing were significantly predicted by participants' peripheral CRP levels. Similarly, depressive symptoms after exposure to an in vivo immune challenge was con-

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tingent, at least in part, on a reduction in ventral striatum activity in response to anticipated rewards.¹⁴⁷ These findings parallel the results of neuroimaging studies showing that administration of interferon- α , a potent proinflammatory cytokine, led to reduced activity in the ventral striatum during a hedonic reward task.¹⁴⁸ Moreover, positron emission tomography was utilized to show an interferon- α -induced increase in ¹⁸F-dopa (radiolabeled dopamine precursor) uptake, but decreased ¹⁸F-dopa turnover, in the basal ganglia, which correlated with increased depressive symptoms.¹⁴⁸ Together, these findings suggest that inflammation may adversely impact motivation and goal-directed behavior by decreasing activation and connectivity of brain regions involved in processing of rewarding stimuli and psychomotor speed, plausibly through the modulation of dopamine function.

The recent understanding of the above interactions between stress and inflammation has given rise to research that applied these findings to both new and longstanding treatment approaches. For instance, there is a growing body of research that suggests that cognitive-behavior therapy (CBT) reduces inflammation in the context of improving disturbed sleep and depressed mood.^{149,150} Other treatment approaches, such as mindfulness meditation and yoga, are also associated with decreased stress-induced inflammation.^{151,152} Finally, there is evidence in human clinical populations that targeting inflammation directly may help to alleviate symptoms of psychopathology, including MDD, PTSD, and schizophrenia, but only in a subgroup of patients who exhibit increased initial levels of inflammatory markers.¹⁵³⁻¹⁵⁸ Specifically, meta-analyses have supported the beneficial use of anti-inflammatory medication in schizophrenia-affected individuals, particularly those who are in the early stages of this disorder.^{158,159} Although preliminary results of the anti-inflammatory therapy in the treatment of psychiatric disorders are promising, it is important to identify specific subgroups that would benefit the most from such treatment.¹⁶⁰ For example, one study examined the potential antidepressant effect of the TNF- α inhibitor infliximab in patients with treatment-resistant depression who were otherwise healthy. Infliximab is a monoclonal antibody directed against TNF- α that prevents this cytokine from binding to its receptor via immunoneutralization. Interestingly, the anti-inflammatory therapy outperformed placebo, but only in patients with high peripheral levels

of CRP before treatment (>5 mg/L).¹⁶¹ Baseline levels of inflammation could, therefore, serve as a biomarker of an individual's likelihood of responding to anti-inflammatory therapies. Intriguingly, among participants with a baseline CRP value greater than 5 mg/L, anti-inflammatory therapy led to a reduction in a variety of symptoms, including sad mood, psychomotor retardation, anhedonia, anxiety, and suicidal ideation, all of which are linked to the neurocircuits typically targeted by inflammatory cytokines.¹⁶¹ Overall, therefore, anti-inflammatory therapy may be a promising treatment for specific subgroups of patients with a variety of psychiatric disorders, such as those with elevated circulating inflammatory markers. The identification of, and ability to detect, specific biomarkers that can identify individuals who would benefit from anti-inflammatory therapy is a critical step in delivering individualized therapy.

Despite recent advances made in understanding the role of inflammatory processes in human psychopathology, direct evidence examining potential sex differences is only recently being addressed. Historically, men and women have been known to display pronounced biological and psychological differences in responses to stress, with females typically displaying nearly double the GC response relative to males.¹⁶² Stress reactivity is also not constant across developmental epoch or across hormonal cycles; women who are between the ages of puberty and menopause typically exhibit lower HPA-axis and autonomic nervous system responses to acute psychosocial stressors than older women. However, the intensity of responses increases in the luteal phase and after menopause.¹⁶³ What is striking is that women have higher rates of stress-related psychiatric disorders that have been strongly linked to inflammation, including MDD and anxiety disorders.¹⁶⁴ This sex difference in depression is evident across Western and non-Western cultures.¹⁶⁵ The sex-specific epidemiological pattern of psychiatric disorders highlights the role of sex hormones in stress reactivity, since many of these sex differences emerge in puberty. Interestingly, there is also evidence of sexual dimorphism in the susceptibility of women and men to immune-related disorders. For instance, the prevalence of many inflammatory conditions, including autoimmune diseases is significantly higher in women,¹⁶⁶ whereas men are more likely to suffer from infectious diseases.¹⁶⁷ Notably, young women were reported to exhibit higher peripheral levels of IL-6 than men after mental or physical stress.¹⁶⁸ Clearly,

more research is needed in this area, as it may be that sex differences in stress reactivity, including inflammatory and, potentially, neuroimmune responses to stress, could provide much needed insight into the vast sex differences in the rate of stress-related psychiatric disorders.

Conclusion

The goal of this review was to highlight the neuroimmune mechanisms underlying the response to stress with an emphasis on extending findings from animal models toward the human experience. Research on rodents has served as a starting point for understanding the molecular and cellular responses to stress, allowing for a greater understanding of how inflammatory factors, such as cytokines, chemokines, and prostaglandins, ultimately influence brain function. Importantly, microglia have emerged as a key interface between stress-related signals and neuroimmune consequences of stress. The guinea pig in particular serves as a useful model of early-life stress with excellent early-life translatability that recapitulates findings from nonhuman primates and humans. Further validation of the guinea pig model, and expansion of genetic tools and antibodies directed toward guinea pig-specific proteins, will allow for bridging the findings in rats and mice with a complementary, tractable model system. The use of nonhuman primates confers significant advantages not only in being able to bridge findings in rodent models to humans, but also in that they lead highly social lives allowing for examination of stress and social interactions (eg, buffering effect of a cage partner on social separation discussed earlier in the review¹¹⁷). Through

studying conserved transcriptional responses to stress that have been examined in circulating leukocytes in humans, researchers have made connections between clinically relevant psychological disorders and expression levels of immune and inflammatory factors.^{133,136} The finding that epigenetic modulation of cytokines differs in individuals with stress-related disorders, such as MDD and PTSD,¹³⁸ provides an intriguing avenue for animal model research in examining how stress can affect future gene expression. Thus, viewing neuroimmune consequences of stress through a multispecies lens provides a compelling argument for the highly conserved nature of the relationship between cytokines, stress, and multiple forms of psychopathology. Our challenge for the future, therefore, will be to dive deeper into individual differences in stress reactivity, using a combination of highly tractable animal models from different species to better discriminate between those neuroimmune consequences of stress that are constant within and across species, relative to those that differ as a function of the individual (sex, age, recent stress history) or that are species-specific. In doing so, we can exploit the strengths of individual model systems while at the same time circumventing their limitations, with the hope of defining novel therapeutic strategies to ameliorate adverse health consequences of stress. □

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Una aproximación multi-especies para comprender el mecanismo neuroinmune del estrés

Actualmente está bien establecida la relación entre los efectos del estrés y los resultados adversos sobre la salud, especialmente para el desarrollo de los trastornos afectivos. Los mecanismos neuroinmunes, muy bien conservados entre las especies, y a través de los cuales las respuestas a los estresores se traducen en efectos sobre hombres y mujeres, han generado recientemente gran atención tanto para los investigadores como para los clínicos. El empleo de modelos animales, desde ratones y cobayos, hasta primates, ha mejorado enormemente nuestra comprensión acerca de estos mecanismos a nivel molecular, celular y conductual. La investigación en humanos ha identificado regiones y conexiones cerebrales de interés, como también asociaciones entre la inflamación producida por el estrés y los trastornos psiquiátricos. Esta revisión reúne hallazgos en múltiples especies para una mejor comprensión de cómo contribuyen los mecanismos de la respuesta neuroinmune a las psicopatologías relacionadas con el estrés como el trastorno depresivo mayor, la esquizofrenia y el trastorno bipolar.

Une approche multi-espèces pour comprendre le mécanisme neuro-immunitaire du stress

Les effets nocifs du stress sur la santé sont maintenant bien connus, en particulier en ce qui concerne le développement des troubles affectifs. Les mécanismes neuro-immunitaires très bien conservés parmi les espèces et par lesquels les réponses aux facteurs de stress se répercutent sur les hommes et les femmes ont récemment suscité une attention particulière des chercheurs et des cliniciens. L'utilisation de modèles animaux, de la souris au cobaye et jusqu'aux primates, a considérablement amélioré notre compréhension de ces mécanismes aux niveaux moléculaire, cellulaire et comportemental. La recherche chez l'homme a permis d'identifier des régions cérébrales particulières et des connexions intéressantes, ainsi que des associations entre l'inflammation induite par le stress et les troubles psychiatriques. Cet article fait la synthèse des données de nombreuses espèces afin de mieux comprendre comment les mécanismes de la réponse neuro-immunitaire au stress contribuent aux psychopathologies liées au stress, comme les troubles dépressifs caractérisés, la schizophrénie et les troubles bipolaires.