

Social neuroscience and health: neurophysiological mechanisms linking social ties with physical health

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Although considerable research has shown the importance of social connection for physical health, little is known about the higher-level neurocognitive processes that link experiences of social connection or disconnection with health-relevant physiological responses. Here we review the key physiological systems implicated in the link between social ties and health and the neural mechanisms that may translate social experiences into downstream health-relevant physiological responses. Specifically, we suggest that threats to social connection may tap into the same neural and physiological 'alarm system' that responds to other critical survival threats, such as the threat or experience of physical harm. Similarly, experiences of social connection may tap into basic reward-related mechanisms that have inhibitory relationships with threat-related responding. Indeed, the neurocognitive correlates of social disconnection and connection may be important mediators for understanding the relationships between social ties and health.

It is well established that social relationships are important for physical health. Relative to socially isolated individuals, socially connected individuals live longer¹ and show increased resistance to a variety of somatic diseases ranging from heart disease to cancer². Considerable research has linked the absence or presence of social connections to altered activity of neural and endocrine systems that affect disease pathophysiology, such as the sympathetic nervous system (SNS) and the hypothalamus-pituitary-adrenal (HPA) axis. A growing body of research has followed these dynamics downstream to chart their effect on disease-regulating biological processes, such as immune cell gene expression and inflammatory dynamics³, which can contribute to disease (for example, metabolic disease, atherosclerosis and tumor metastasis) and mortality^{2,4}. Still, how social connections modulate the physiological underpinnings of disease is not yet clear. This article integrates findings from social and affective neuroscience to highlight the upstream neurocognitive processes that may translate the presence or absence of social ties into these

physiological responses that affect physical health (see ref. 5 for a discussion of the neural processes relevant to mental health).

Overview of the mechanisms that link social ties with health

The study of social relationships and health has typically treated the presence versus the absence of social ties as two ends of the same spectrum, such that having social ties is associated with health benefits, whereas lacking social ties is associated with health decrements⁶. Similarly, subjective assessments of social ties, which in some cases have stronger relationships with health-relevant variables^{1,6}, have been placed on this same uni-dimensional scale. Perceived social support or social connection (the perception that one is cared for, loved and valued by others) predicts better health outcomes, whereas loneliness or social disconnection (the perception that one is socially isolated or not connected to others) predicts poorer health outcomes^{1,6}. Although perceptions of social connection or disconnection may ultimately influence health through the same peripheral 'distributors' of social psychological experience (SNS and HPA axis), these social experiences may engage multiple, functionally distinct neural circuits in the central neural and neurobiological systems. We suggest that discrete experiences of social disconnection versus connection may be processed by separate neural systems involved in responding to harm and reward, respectively, resulting in corresponding peripheral physiological responses that represent an integration of output from those two central neural systems.

First, based on the importance of social ties for survival in many social species⁶, experiences of social disconnection may be processed as a fundamental survival threat⁶⁻⁸. Consequently, cues that signal that one's connections to others are threatened or damaged (which will vary as a function of individual sensitivities and contextual factors⁶) may activate a basic 'neural alarm system' that detects and elicits adaptive responses to impending danger or harm. This neural alarm system includes the amygdala, which is well known for its role in threat-related responding, as well as the dorsal anterior cingulate cortex (dACC), anterior insula and periaqueductal gray (PAG), which are known for their roles in both threat- and pain-related processing (Fig. 1a). Regions in this neural alarm system can activate autonomic and endocrine responses that have implications for health. Although the experience of social disconnection (for example, through exclusion) may be somewhat different than the possibility of social disconnection (for example, through social evaluation), these two constructs are grouped together here, as not enough research is available to make separate predictions.

Second, to the extent that having social ties benefits survival^{6,9}, cues that signal that one is cared for, valued by, or connected to others (which will also vary as a function of individual sensitivities and

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Published online 15 April 2012; doi:10.1038/nn.3086

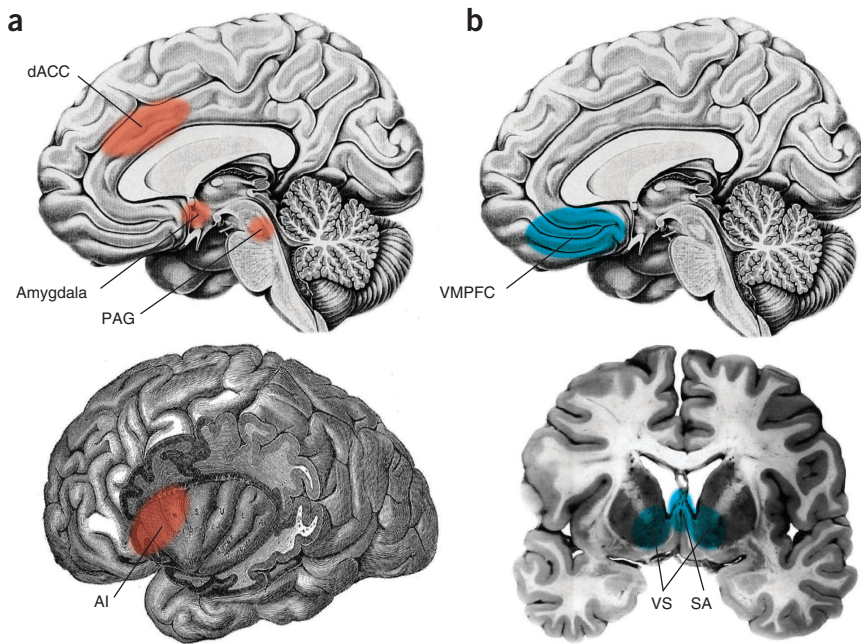


Figure 1 Neural correlates of social disconnection and connection. (a,b) Neural regions hypothesized to be involved in processing social disconnection (red, a) and social connection (blue, b). Threat-sensitive regions involved in processing social disconnection include the amygdala, PAG, dACC (top) and anterior insula (AI, bottom). Reward-sensitive regions involved in processing social connection include the VMPFC (top) and ventral striatum (VS) and septal area (SA, bottom).

contextual factors) may rely on basic reward-related neural regions that reinforce these experiences of social connection. Activation of these reward systems may also help promote the reciprocal provision of care and connection to others. Notably, some of these neural regions have inhibitory relationships with threat-related neural and physiological responding and may have health implications. We focus on two reward-related substrates that may process social connection and inhibit threat-related responding: activity in the ventromedial prefrontal cortex (VMPFC), which tracks the safety value of a stimulus and inhibits threat-related responding¹⁰, and neural and neurobiological responses involved in caregiving behavior (ventral striatum, septal area, opioids and oxytocin), which reduce threat responding to facilitate adaptive caregiving during stress⁹ (Fig. 1b). Before elaborating on these systems, we first review the important physiological systems that link social ties with physical health.

Physiological systems that link social ties and health

Mechanistic analyses have identified several common pathways by which social conditions (that is, social connection and disconnection) can affect the development and progression of a diverse array of specific diseases. The most central of these pathways involves the common role of inflammation in promoting most chronic diseases of aging, including atherosclerosis, Type II diabetes, neurodegeneration and tumor metastasis⁴, and the brain's capacity to regulate inflammatory gene expression via the SNS and HPA axis³. Indeed, threats to social connection can activate both of these systems^{11,12}. However, different types of social threat may engage one system more strongly than the other because HPA axis and SNS responses are maximally triggered by somewhat different psychological experiences (for example, severe overwhelming threat versus anticipated threat or challenge)¹³. Notably, in addition to their differential engagement by different psychological states and social circumstances, the SNS and HPA axis also exert different effects on inflammatory biology.

Acute SNS signaling through beta-adrenergic receptors on immune cells enhances the expression of pro-inflammatory cytokine genes, such as *IL1B* and *IL6*, whereas acute HPA axis activation potentially represses those genes (Fig. 2).

In addition, persistent activation of these systems, as might be expected in the context of chronic social disconnection, can alter their effects on the immune system. Chronic social disconnection can inhibit the glucocorticoid receptor's ability to transduce HPA axis cortisol signals into anti-inflammatory cellular responses¹⁴. Presumably as a result of this acquired glucocorticoid desensitization, chronic social disconnection or the threat of major social loss in humans is associated with both increased basal levels of inflammatory gene expression in circulating immune cells^{14,15} and increased cellular responses to microbial stimuli². The SNS also shows altered regulatory dynamics in the absence of stable social connections, but these often develop in a sensitizing, rather than desensitizing, direction (as observed for glucocorticoid signaling). For example, in macaques, several months of low-grade social instability can upregulate arboriza-

tion of the SNS nerve fibers that innervate lymph nodes (involved in coordinating immune responses)¹⁶. Moreover, observational studies of humans experiencing chronic social disconnection show elevated pro-inflammatory cytokine levels and increased pro-inflammatory cytokine gene expression^{14,15}.

In addition to inflammation, the SNS and HPA axis regulate a wide variety of other cellular and molecular processes that may contribute to disease incidence or progression, such as antiviral responses (reviewed previously³). Other peripheral neural systems (for example, the parasympathetic nervous system) and endocrine mediators (for example, oxytocin) may also be involved in mediating the effects of social connection on health. However, the SNS and HPA axis are the best-explored peripheral 'distributors' of centrally mediated social experiences. What remains less clear is how those lower/peripheral distribution systems are themselves regulated by higher order neural systems involved in the experience of social connection or disconnection.

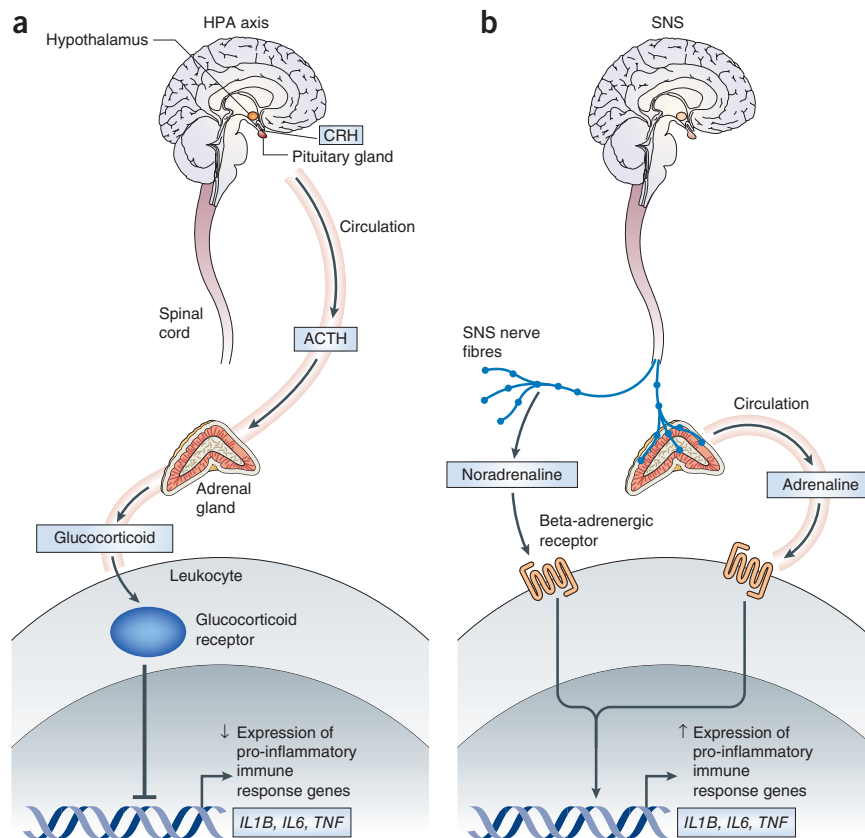
A neural alarm system mediator of the social ties–health link

To the extent that social disconnection is processed as a fundamental threat to survival, the experience or possibility of social disconnection should activate a basic neural alarm system that detects and elicits adaptive responses (emotional, behavioral and physiological) to survival threats. Indeed, animal and human research points to a set of neural regions, including the amygdala, dACC, anterior insula and PAG, that are involved in detecting and responding to impending danger or threat, including the threat of social disconnection.

The amygdala, the most exhaustively studied threat-related region, has been shown to respond to innately threatening stimuli, such as impending pain or an approaching tarantula^{17,18}. It is also involved in fear conditioning, learning contingencies that predict aversive outcomes^{10,19}. Critical for this region's role in health-relevant physiological responses, the amygdala (more specifically, the central nucleus of the amygdala) controls the expression of fear-related

Figure 2 CNS regulation of inflammatory gene expression in immune cells. **(a)** Activation of the HPA axis suppresses pro-inflammatory gene networks (for example, NF- κ B-mediated transcription of pro-inflammatory cytokine genes, such as *IL1B*, *IL6* and *TNF*).

ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone. **(b)** Activation of the SNS leads to the release of the neurotransmitter noradrenaline (from SNS nerve fibers) into primary and secondary lymphoid organs, other major organ systems (vasculature, perivascular tissues), and many peripheral tissues in which pro-inflammatory reactions occur. SNS nerve fibers can also stimulate the adrenal glands to release stored adrenaline into the systemic circulation. Both of these neuromediators can enhance pro-inflammatory cytokine responses and gene expression.



changes in autonomic (SNS) and endocrine responses through projections to the hypothalamus and brainstem areas¹⁰. Stimulating the central nucleus of the amygdala increases blood pressure (reviewed previously¹⁰), and greater amygdala activity during fear acquisition is associated with greater SNS activity (skin conductance response, SCR) to a conditioned stimulus¹⁹ (although the precise nucleus of the amygdala can not be determined in neuroimaging studies). Conversely, lesions to the central nucleus of the amygdala can reduce SNS and endocrine responses to conditioned stimuli¹⁰.

The dACC, anterior insula and PAG are also involved in responding to threat or harm. In addition to processing pain⁸, these regions show increased activity to imminent threat, either from impending pain or an approaching threatening stimulus (spider)^{17,18}. Moreover, the dACC and anterior insula are also routinely activated (sometimes more reliably than the amygdala) during fear conditioning procedures^{19,20}. Consistent with this, rodent studies have found that the prelimbic cortex, homologous with the dACC and dorsal portion of the medial prefrontal cortex (DMPFC, Brodmann Area (BA) 8/9) in humans, is involved in sustaining fear or threat responses²¹, possibly through excitatory projections to the amygdala²⁰. In addition, similar to the amygdala, these regions can alter SNS activity. Electrical stimulation of the dACC induces SCRs, whereas lesions to the dACC reduce SNS responses^{20,22}. PAG activity can increase or decrease SNS responding depending on the type of stressor (for example, escapable or inescapable) and the specific PAG column activated²³. The anterior insula, on the other hand, while often associated with SNS activity, may be more involved in representing autonomic responses in conscious awareness than in generating these responses²⁴.

Notably, experiences of social disconnection rely on some of these same basic neural alarm system substrates⁸. For example, experiences of social exclusion or social rejection activate the dACC and anterior insula^{7,25}. Similarly, threats to social connection in the form of negative social feedback activate the dACC, anterior insula and DMPFC²⁶. In addition, viewing images of recently deceased loved ones activates the dACC, anterior insula and PAG²⁷ (a full description of the studies examining the neural correlates of social disconnection is provided elsewhere⁸). Supporting a causal role for these regions in contributing to states of social disconnection, lesioning the dACC or PAG in young animals reduces distress

vocalizations following maternal separation, whereas stimulating these regions leads to the spontaneous production of these vocalizations²⁸. Notably, although social disconnection activates many alarm system regions, it does not typically activate the amygdala. One explanation for this is that the amygdala may be more involved in responding to concrete cues that predict negative outcomes (for example, angry or disapproving faces), rather than more complex socioemotional inputs that involve appraisals of social connection (for example, interpreting a lack of attention as rejecting). Indeed, higher level neural regions, such as the dACC and nearby DMPFC, may be critical for translating complex socioemotional experiences, such as exclusion or negative social feedback, into threat-related physiological responding.

Triangulating across the neural correlates of threat, social disconnection and physiological responding, emerging evidence highlights the involvement of this neural alarm system in physiological responses to social threats (involving the experience or possibility of social disconnection). With regard to autonomic responses, tasks that threaten intellectual competence (possibly comprising an individual's sense of self-worth and potential for social connection) lead to increased dACC and anterior insula activity, which correlates with increased cardiovascular and SNS activity^{22,29,30}. Similarly, greater dACC and PAG activity in response to social-evaluative stress (involving the possibility of social disconnection as a result of negative evaluation) correlates with increased heart rate³¹. In addition, patient studies suggest that the dACC is involved in generating these autonomic responses to higher-level stressors, as patients with dACC damage show blunted SNS activity, particularly to mental stress²².

Explorations of the neural correlates of cortisol (HPA-related activity) and inflammatory responses to social threat, although more scarce, reveal consistent findings. Greater dACC activity correlates

with increased cortisol levels in response to mental stress³². Greater dACC and DMPFC (BA 8) activity in response to social exclusion is associated with greater cortisol reactivity to a similar social stressor³³. In addition, in the one study to examine the neural correlates of inflammatory responses to social stress, greater dACC and anterior insula activity in response to social exclusion was associated with greater inflammatory responses to a similar social stressor³⁴. Finally, linking threat-related neural activity to actual disease outcomes, animal studies have shown that lesions to two neural regions, the dACC and amygdala, attenuate threat-induced gastric pathology (for example, inflammatory-related gastric ulcers)³⁵. Similarly, dACC lesions in humans have been shown to alleviate gastrointestinal ulcers³⁵. Thus, certain survival threats, including the experience or possibility of social disconnection, may relate to health through alarm system-related neural and physiological responding.

A neural reward system mediator of the social ties–health link

In addition to a neural alarm system that is sensitive to social disconnection, the human mind may also be equipped with a separate system that is sensitive to social connection. Indeed, to the extent that social connection benefits survival^{16,9}, experiences of social connection may rely on basic reward-related circuitry that reinforces social relationships. Importantly for health, some reward-related circuitry has been shown to reduce threat-related physiological responding. Here we focus on two types of reward-related mechanisms that may link social ties with health: neural regions that process safety and reduce threat-related responding¹⁰, and neural regions and neuropeptides involved in caregiving behavior that reduce threat-related responding to facilitate responsive caregiving during stress⁹.

Safety-related processing. The health-protective benefits of the presence of social support during stress may rely, in part, on neural regions involved in detecting safety and reducing fear. Indeed, critical to survival is the ability to detect, not only danger and harm, but safety and security (for example, presence of a support figure), which may be experienced as rewarding or reinforcing. Along these lines, considerable research has implicated the VMPFC, a reward-related region, as well as the posterior cingulate cortex (PCC), in responding to cues that signal safety¹⁰. For example, moving a tarantula a safe distance away from a subject's foot is associated with increased VMPFC and PCC activity¹⁸. In addition, fear extinction, a form of 'learned safety' in which a cue that previously predicted a negative outcome (for example, shock) now predicts safety (for example, no shock), also activates these regions^{10,19}. Notably, VMPFC activity reduces fear responding through inhibitory connections with the amygdala¹⁰. Thus, stimulating the infralimbic cortex in rats, homologous to VMPFC (BA 11) and subgenual anterior cingulate cortex (subACC, BA 25) in humans, diminishes fear responding to fear cues³⁶, and greater VMPFC activity is associated with reduced fear responding (SCRs) in humans^{10,19}. Moreover, in addition to responding to safety in the context of fear, the VMPFC and PCC also appear to be responsive to safety in the context of pain and stress (showing greater activity to conditions of low, as opposed to high, pain or stress, which are presumably safer)^{31,37,38}.

Notably, activity in these regions has been shown to correlate with reductions in autonomic and endocrine responding. For example, VMPFC and PCC activity during mental or social stress correlates negatively with cardiovascular activity^{29–31} and threat-related neural activity (dACC, PAG)³¹. In addition, greater activity in the VMPFC and subACC is associated with increases in parasympathetic responding, which is in turn associated with reduced cardiovascular arousal³⁹. Thus,

activity in these safety-related regions may be involved in inhibiting sympathetic and promoting parasympathetic responses, which may be health protective. In addition, greater activity in these regions is also associated with reduced cortisol responses to social stress^{33,38}, and damage to the VMPFC increases feelings of threat and cortisol responses (for females) in response to social stress⁴⁰. Finally, highlighting a causal role for these regions in inhibiting threat-related disease outcomes, lesioning either the VMPFC or PCC in animals leads to increases in threat-induced gastric pathology (inflammatory-related gastric ulcers)³⁵.

Although little research has examined the neural mediators that link social connection with physiological responses, preliminary research has demonstrated that being reminded of one's social connections can activate these safety-related neural regions and may therefore have health implications. For example, seeing a picture of a highly supportive, romantic relationship partner during the experience of physical pain leads to increased VMPFC activity and corresponding decreases in self-reported pain and dACC activity⁴¹. Similarly, being provided with socially supportive messages during social exclusion leads to increased activity in the VMPFC and PCC⁴². Future work will be needed to determine whether social support attenuates physiological stress responses through these safety-related neural regions.

Caregiving-related processing. An additional pathway that may be relevant for understanding the health benefits of social connection involves the reward-related substrates implicated in caregiving behavior. Engaging in caregiving behaviors, such as providing support or care to offspring or loved ones, is associated with reduced cardiovascular arousal⁴³ and lower mortality rates⁴⁴. This may be partly a result of reward-related neurobiological pathways that inhibit threat-related responding in the context of caregiving. Indeed, it has been suggested that caregiving may reduce threat-related responding to facilitate responsive caregiving during times of stress, thus promoting offspring and kin survival⁹.

Caregiving behavior in animals relies on reward-related neural regions, including the ventral striatum and septal area⁹. Notably, the septal area has been shown to reduce threat-related responding through inhibitory connections with the amygdala⁴⁵. Thus, stimulating the septal area decreases SNS activity, whereas lesioning the septal area increases SNS and HPA responses to stress⁴⁵. Consistent with this, human research has shown that providing support to a loved one in need increases feelings of social connection as well as ventral striatum and septal area activity; moreover, greater septal area activity during support-giving is associated with reduced amygdala activation⁹, which may have implications for reduced SNS and HPA responses.

Although not fully understood, these neural processes may be mediated in part by neuropeptides involved in social bonding, such as endogenous opioids and oxytocin, which are released in response to positive close social contact (as well as stress)^{28,46} and have stress-reducing properties. Consistent with this, the ventral striatum and septal area (as well as the amygdala) have high densities of opioid and/or oxytocin receptors^{47,48}. Moreover, opioids attenuate SNS and HPA activity, reduce conditioned fear responses and enhance fear extinction⁴⁹. Opioids are also potent immunomodulators, inhibiting the production of pro-inflammatory cytokines⁵⁰. Similarly, oxytocin reduces SNS and HPA responses, and may do so in part via opioid-related activity⁴⁶. Future work will be needed to determine whether caregiving-related substrates contribute to the health benefits of social connection.

Conclusions

Research over recent decades has made clear the importance of social relationships for physical health^{1–3}. What is less clear, however, is why the external ‘macro’ social world should be capable of affecting the internal ‘micro’ cellular and molecular processes that mediate health and disease. The merging of social neuroscience and immunological perspectives provides a few possible answers to this question.

From a social neuroscience perspective, the brain is equipped with dedicated neural circuits that have evolved to detect threats to survival (threat/harm-related circuitry) and benefits to survival (safety/reward-related circuitry). To the extent that social connection is another critical ingredient for survival, experiences of social disconnection and connection may have co-opted this basic harm and reward circuitry, respectively. Given that these systems elicit adaptive physiological responses (increasing SNS and HPA responses to threat, decreasing to safety/caregiving behavior), experiences of social disconnection and connection may set in motion these same physiological responses, ultimately resulting in health consequences.

From an immunological perspective, sociality is also important for shaping the nature of microbial threats we confront, and the immune system may have evolved to anticipate this changing pattern of pathogen exposure. Social disconnection leaves individuals vulnerable to physical trauma and wounding (for example, by predators or hostile conspecifics), exposing a profile of wound or trauma-related bacterial infections, which necessitates increased inflammatory responding. Social connection, on the other hand, provides relative protection against such bacterial infections, but at the cost of increased exposure to socially transmitted viruses. As such, the immune system may have evolved to ‘listen in’ on the neural and endocrine correlates of social disconnection to anticipate the nature of the microbial threats it is most likely to confront and to optimally redeploy its genomic resources (for example, up-regulating pro-inflammatory genes to counter wound-related bacterial exposures in isolated or hostile conditions, and down-regulating molecular defenses against socially-transmitted viruses)³.

Although research on the neuroscience of health-relevant processes is beginning to grow, there are several challenges that remain to be addressed. First and foremost is the discrepancy in the time scale of neuroimaging versus health-related studies. Neuroimaging studies focus on neural and physiological responses to discrete social experiences, whereas health-related studies focus on global or chronic assessments of social connection/disconnection and how these measures relate to health outcomes that unfold over time. Consequently, additional research will be needed to understand how discrete social experiences in the scanner combine to comprise more global assessments of social connection/disconnection that are predictive of health outcomes. Moreover, given the importance of chronic social experience (for example, loneliness) for health, additional work will be needed to clarify how long-term exposure to certain social experiences alters the activity or connectivity of the neural systems reviewed here. For example, it is possible that long-term experiences of social disconnection (loneliness) or connection (social support) may fundamentally alter the function and connectivity of these neural systems, consequently affecting how they relate to health-relevant physiological outputs.

Although there are challenges associated with understanding the neural underpinnings of health-relevant physiological responses, neural models also present several pathways that warrant further attention. Along these lines, one of the most fascinating frontiers in this domain involves the role of reward-related circuitry in peripheral gene regulation. Well-defined SNS and HPA pathways link threat/harm

systems with peripheral biology, but much remains to be discovered about the pathways through which social connection might independently regulate the cellular and molecular underpinnings of health.

What is clear, even at this early stage of analysis, is that social connections reach deep into the body to regulate some of our most fundamentally internal molecular processes. Social neuroscience approaches will be important for deciphering both how and why social relationships are critical for health.

COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

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