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Social ties and health: a social neuroscience perspective

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Research over the last several decades has shown that the health of the body is intimately tied to the strength of our social connections, but why? This article reviews evidence from affective and social neuroscience suggesting that, because of the importance of social ties for mammalian survival, threats to social connection are processed by some of the same neural regions that process basic threats to survival and consequently trigger physiological threat responses that have negative health implications. Likewise, social support is processed by some of the same neural regions that process safety or protection from basic threats and inhibit these same health-relevant physiological threat responses.

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Introduction

The mammalian nervous system has evolved with an incredible capacity to respond to threats to survival. In response to basic threats to survival — such as predators, environmental dangers, or injuries — the body responds with a coordinated set of physiological responses that increases chances of survival. For example, threats to survival trigger the activation of the sympathetic nervous system (SNS), implicated in the fight-or-flight response, and the hypothalamic-pituitary-adrenal (HPA) axis, involved in mobilizing energy resources for dealing with long-lasting threats. Each of these systems then has downstream effects on the immune system, possibly preparing the body for dealing with the increased likelihood of wounding associated with these threats. For example, increased SNS activity upregulates inflammatory activity, the body's first line of defense against foreign agents [1,2•]. However, the body's ability to adapt to acute threats in the short-term has also been credited as the cause of the long-term negative health effects of stress. Thus, chronic, threat-related increases in inflammatory activity can contribute to the development of various inflammatory-related diseases (diabetes, atherosclerosis) as well as mortality [3,4].

Interestingly, over the past several decades, research has shown that, like basic threats to survival, threats to social connection can have similar effects on these health-relevant physiological responses. For example, in response to a social-evaluative stressor (such as the Trier Social Stress Test [5]), which involves the possibility of being socially rejected or devalued while delivering a public speech, subjects show increases in SNS, HPA, and inflammatory responding [6,7]. Additionally, relative to those who feel socially connected, individuals who feel lonely or socially disconnected show enhanced proinflammatory gene expression [8••]. Indeed, the fact that social experience can alter physiological stress responses is thought to be one contributor to the strong links between a lack of social ties and mortality.

One obvious question that stems from these observations is: why? Why are the same survival-related responses triggered by basic threats to survival also triggered in response to delivering a public speech? Why would the dynamics of the immune system 'care about' or change in response to whether an individual feels lonely or not? In sum, why would the health of the body be sensitive to the social world?

One provocative hypothesis that may account for the body's inherent sensitivity to the social world stems from the dangers associated with being alone. Given the importance of social connection for mammalian survival, the brain may have evolved to interpret threats to social connection as basic survival threats, resulting in similar physiological stress responses. Hence, threats to social connection, such as being excluded from the social group or rejected by someone, may trigger basic SNS and HPA stress responses because of the increased risk associated with being on the outskirts of the social group. Because being disconnected from the social group makes an individual more vulnerable to attack (by predators or hostile con-specifics) and thus increases the likelihood of wounding and infection, the immune system may have evolved to anticipate situations indicative of social disconnection by increasing inflammatory activity to prepare for these situations in which wounding and infection is more likely [2•,9].

This review integrates recent research from social, affective, and health neuroscience to begin to explore this hypothesis, namely that social ties may influence health,

in part, through the activation of neural systems involved in detecting the presence of basic survival threats or the absence of such threats (safety) and triggering or inhibiting, respectively, health-relevant physiological responses. This article first outlines a set of neural regions involved in processing basic survival threats — stimuli associated with the possibility of physical harm or pain (e.g. predators, environmental dangers, injuries) — and eliciting downstream physiological stress responses. This article then reviews evidence showing that these same regions also respond to threats to social connection — experiences that threaten one's sense of social connection or social value (e.g. being rejected by someone, being excluded from a group, losing a loved one). This article then outlines a set of neural regions involved in processing safety — the relative absence of stimuli associated with physical harm or pain or the presence of stimuli that are protective from harm or pain — and inhibiting downstream physiological stress responses. Finally, this article summarizes preliminary research showing that these regions are also activated in response to receiving social support during times of need.

Basic threat mechanisms as a possible mediator of the link between threats to social connection and health

Neural regions involved in processing threat or harm

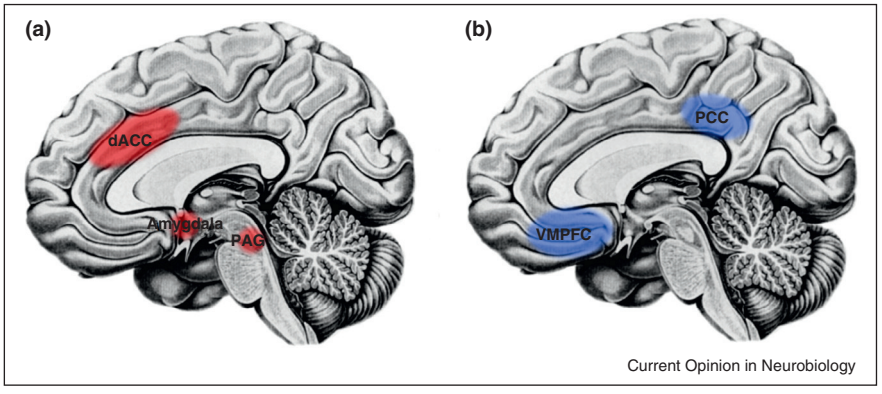
Research on fear and pain processing has highlighted a set of neural regions involved in detecting and responding to basic survival threats. These regions include (but are not limited to) the amygdala, dorsal anterior cingulate cortex (dACC), anterior insula (AI), and periacqueductal gray (PAG) (see Figure 1a).

The amygdala, likely the most well-studied neural region in the context of threat processing, is involved in responding to basic threats, such as impending pain (e.g. shock) and dangerous stimuli (e.g. snakes, spiders, threatening faces) [10,11••,12]. The amygdala, in particular the central nucleus of the amygdala [13•], also plays a critical role in both the acquisition and expression of conditioned fear, a process by which an individual learns associations that predict threatening stimuli [14,15]. Similarly, the dACC, AI, and PAG, though predominantly associated with pain processing [16] also respond to impending pain or imminent threat [11••,17,18] and are reliably activated during fear conditioning paradigms [14,19,20]. Indeed, rodent studies demonstrate that the prelimbic cortex, homologous with the dACC and the nearby dorsomedial prefrontal cortex (DMPFC; Brodmann area 8/9) in humans, is involved in sustaining fear responses [21•,22], possibly through excitatory projections to the amygdala [20,23].

In response to detecting threat, many of these neural regions facilitate downstream physiological responses. The central nucleus of the amygdala controls the expression of fear-related changes in sympathetic and endocrine responses, through projections to the hypothalamus and brainstem areas [21•,24]. Hence, stimulating the central nucleus of the amygdala increases blood pressure [25], whereas lesions to this region reduce sympathetic and endocrine responses to conditioned stimuli [26–29]. Likewise, electrical stimulation of the dACC increases SNS responses [20,30], whereas lesions to the dACC reduce SNS responses [31]. PAG activity can increase or decrease SNS responding depending on the type of stressor (e.g. escapable, inescapable) and the specific PAG column activated [32]. The AI, 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 responses [33••].

Finally, emphasizing the role of these threat-related neural regions in physiological responding that has implications for health outcomes, animal studies have

Figure 1



(a) Neural regions that have been shown to process threat or harm (displayed in red) include the amygdala, dorsal anterior cingulate cortex (dACC), periacqueductal gray (PAG), and anterior insula (not shown here). **(b)** Neural regions that have been shown to process safety (displayed in blue) include the ventromedial prefrontal cortex (VMPFC) and posterior cingulate cortex (PCC). (figure adapted from [9]).

shown that lesions to only two neural regions — the amygdala and ACC — were found to reduce inflammatory-related gastric pathology associated with restraint stress [34]. Similarly, dACC lesions in humans have been shown to alleviate inflammatory-related gastrointestinal ulcers [34].

Neural regions involved in processing threats to social connection

Interestingly, many of the same regions that process basic survival threats also process threats to social connection. For example, experiencing an episode of social exclusion or reliving an experience of social rejection activates the dACC and AI [35,36••,37,38]. Similarly, threats to social connection in the form of negative social feedback activate the dACC, AI, and DMPFC [39]. In fact, simply viewing rejection-themed images increases activity in the amygdala as well as the dACC and AI, particularly for rejection-sensitive individuals [40,41]. Finally, viewing images of recently deceased loved ones activates the dACC, AI, and PAG [42–44]. Thus, various experiences that threaten social connection — from rejection to bereavement — can activate these threat-related neural regions.

Importantly, activity in several of these regions appears to track the subjective experience of social disconnection. Thus, individuals who tend to feel more social distress (more rejected, disconnected) following social exclusion show greater activity in the dACC and AI [36••]. Likewise, individuals who tend to feel more socially disconnected in their real-world interactions show greater activity in the dACC, amygdala, and PAG during social exclusion [45]. The finding that threat-related neural activity tracks the subjective experience of social disconnection maps nicely onto health research, which has shown that subjective assessments of social isolation (e.g. loneliness) often have stronger relationships with physiological stress responses and health outcomes than objective assessments (e.g. network size) [8••,46••,47]. Hence, subjective experiences of social disconnection and the underlying threat-related neural response may be critical for understanding how social experience influences health.

Neural mediators of the link between threats to social connection and physiological responses

In addition to showing that threats to social connection can activate basic threat-related neural regions, several studies have also shown that activity in the these regions correlates with physiological stress responding. For example, various types of cognitive performance tasks (e.g. mental arithmetic) that involve elements of social evaluation or threats to intellectual competence (and thus imply the possibility of negative social evaluation or social rejection) increase autonomic activation (heart rate, blood pressure). When examining neural predictors of these autonomic changes, greater activity in the dACC, AI, and in some cases, the amygdala in response to these stressors is associated with greater increases in autonomic activation (e.g. increases in blood pressure, heart rate, pupil dilation) [31,48–51]. In fact, the dACC, in particular, may play a role in generating these autonomic responses to mental stressors, as patients with dACC damage show blunted autonomic responses, particularly to mental stressors [31]. Indeed, a recent study demonstrated that, in response to a social-evaluative stressor (preparing to give a public speech), greater activity in the dACC as well as the PAG was associated with greater increases in heart rate [52••].

Although more is known about the neural correlates of autonomic responses to stress, studies examining the neural correlates of neuroendocrine and inflammatory responses have revealed consistent findings. Greater activity in the dACC following a mental stress task was associated with greater increases in cortisol [53], particularly for females [54]. Similarly, greater activity in the dACC and nearby DMPFC in response to social exclusion was associated with greater increases in cortisol to a similar social stressor [45]. Likewise, individuals who showed an increase in cortisol (versus those who did not) to a social-evaluative stressor showed increased activity in the DMPFC [55]. Finally, in the one study to examine the neural correlates of inflammatory responses to social stress, greater dACC and AI activity in response to social exclusion was associated with greater inflammatory responses to a similar social stressor [56•]. Thus, threats to social connection may relate to health through increased threat-related neural and physiological stress responding.

Basic safety mechanisms as a possible mediator of the link between social connection and health

Neural regions involved in processing safety

In addition to a set of neural regions involved in processing threat, the brain is also equipped with a set of neural regions that process 'safety' — the relative absence (versus presence) of threat or the presence of stimuli known to be protective from threat — and reduce threat responding to these contextual safety cues. In fact, research has highlighted the involvement of the ventromedial prefrontal cortex (VMPFC), a region often associated with reward [57], and, in some cases, the posterior cingulate cortex (PCC) (see Figure 1b), in responding to cues that signal safety or the absence of negative outcomes (relative to the presence of negative outcomes) [15,21•], and thus may be experienced as rewarding. For example, moving a live tarantula away from (versus closer to) a subject's foot was associated with increased activity in the VMPFC and PCC [11••]. Similarly, learning that a cue that previously predicted a negative outcome (e.g. shock) now predicts safety (e.g. no shock), a process called

fear extinction or learned safety, also activates these regions [14,20,21•].

In addition to detecting conditions of increasing safety, the VMPFC also plays a role in inhibiting threat-related behavioral and physiological responding [21•]. In animals, the infralimbic cortex — homologous to VMPFC (BA 11) and nearby subgenual anterior cingulate cortex (subACC; Brodmann area 25) in humans — is critical for detecting safety and reducing fear responding through inhibitory connections with the amygdala [15]. As such, stimulating the infralimbic cortex in rats inhibits the central nucleus of the amygdala [58] and diminishes fear responding to fear cues [59].

Similarly, human neuroimaging studies have shown that greater activity in these regions is associated with reductions in threat-related physiological responding. Greater VMPFC activity during fear extinction (safety learning) is associated with reduced SNS activity [14,21•]. Greater VMPFC and PCC activity during mental or social stress is associated with reduced cardiovascular responding [33••,49,52••,60] as well as reduced threat-related neural activity (dACC, PAG) [52••]. Finally, greater activity in these regions is also associated with reduced cortisol responses to social stress [45,61], and damage to the VMPFC increases feelings of threat and cortisol responses (in females) in response to social stress [62]. Finally, as evidence for a causal role for these regions in inhibiting threat-related disease outcomes, lesioning either the VMPFC or PCC in animals leads to increases in inflammatory-related gastric pathology [34].

Interestingly, consistent with the hypothesis that these regions may reduce threat-responding, possibly to promote rest and restoration in response to safety, a recent meta-analysis showed that the VMPFC/subACC is associated with parasympathetic nervous system activity [63], a component of the autonomic nervous system involved in reducing physiological arousal and promoting vegetative activities that occur when the body is at rest (digestion, growth). Thus, activity in these safety-related regions may be involved in promoting parasympathetic and inhibiting sympathetic responses, which may ultimately be health-protective.

Neural regions involved in processing social connection or social support

Although research on the neural underpinnings of social connection and social support is still in its infancy, some work is beginning to show that some of the same neural regions that detect safety and reduce threat are also involved in responding to the presence of a social support figure during stress. For example, two studies have shown that seeing a picture of a highly supportive relationship partner while experiencing physical pain leads to increased activity in the VMPFC and/or PCC as well as decreased activity in the dACC and insula [64•,65]. Moreover, consistent with the role of the VMPFC in reducing threat-related responding, both studies demonstrated that greater activity in the VMPFC was associated with reductions in self-reported pain [64•,65], and in one study, greater VMPFC activity was associated with reduced pain-related neural activity in the dACC [64•].

Similar results were observed in a study examining social support during a negative social experience. Being provided with socially supportive messages while experiencing social exclusion (versus social inclusion) led to increased activity in the VMPFC and PCC and reduced activity in the insula [66]. Along these lines, thinking about close others versus strangers, though not during a negative experience, also activates the VMPFC and PCC [67,68]. Still, some studies showed that the presence of social support reduced activity in certain threat-related neural regions but did not increase activity in other regions [69,70]. In addition, studies examining how general perceptions of social support (e.g. tendency to interact with supportive others on a daily basis) relate to neural responses to threatening events show reduced activity in threat-related neural regions but no increased activity in other regions [45,71,72]. Thus, additional work will be needed to better understand the neural underpinnings associated with the threat-reducing effects of social support. Future work will also be needed to examine whether the presence of social support attenuates health-relevant physiological responding through these safety-related neural regions.

Conclusions and future directions

In sum, research is beginning to highlight some of the ways in which social experience relates to health by examining the neural mechanisms that translate social connection or a lack thereof into health-relevant physiological responses. This review outlined threat-related and safety-related neural regions and demonstrated that these same regions are responsive to the absence or presence of social connection, respectively. Together, these findings underscore the importance of social ties for human survival and highlight the trickle-down effect that this importance may have on our physical health. Specifically, to the extent that lacking social ties increases the risk of wounding and infection, the brain may have evolved to respond psychologically and physiologically to these risky social situations as though they were immediate threats to survival. In contrast, experiences of social connection or social support may serve to quiet these same physiological stress responses through the activation of neural regions that detect safety and inhibit physiological stress responses when they are not needed. Over time, chronic experiences of social disconnection or connection may change the body — by upregulating or downregulating inflammatory dynamics in order to prepare the body for

these social situations in which survival is threatened or benefited, respectively.

Although research on the neural mechanisms linking social experience with health is beginning to grow, there are many questions that remain to be answered within this emerging field. First, in addition to understanding the basic neural regions that facilitate or inhibit physiological stress responses (SNS, HPA) in response to discrete social events, it will also be important to understand how chronic forms of social experience may alter these neural and physiological responses over time. Thus, most health-related research has focused on chronic social experiences (e.g. loneliness, having social ties) that predict health-relevant outcomes or mortality [8••,46••]. It will be important for neuroimaging research, which is adept at identifying neural responses to acute social experience, to begin to assess how chronic or repeated exposure to social experiences affects neural and physiological responding over time. In addition, though not yet widely used, higher-resolution neuroimaging techniques will be necessary to effectively chart out pathways from higher-level neural regions involved in appraising social connection with lower-level neural regions that mediate SNS and HPA responding. Finally, it will be important to better understand whether these same neural regions, critical for physical health, relate to mental health as well. Given the importance of social connection for survival, it seems likely that these same neural regions that process the absence or presence of social connection would also be critically involved in various forms of psychiatric illness. For example, psychiatric disorders that involve social deficits may be most closely linked to altered activity in these regions and may stem, in part, from exaggerated neural responsivity to threats to social connection (e.g. social anxiety, depression), diminished neural responsivity to threats to social connection (e.g. psychopathy, autism), or diminished neural responsivity to social support and safety (e.g. borderline personality disorder, post-traumatic stress disorder). Social neuroscience may provide a critical platform for further understanding the complex relationships between the brain and both physical and mental health.

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