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Social neuroscience: The social brain, oxytocin, and health

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Complex social behaviors allow various social organisms to create emergent organizations that extend beyond the individual. Social neuroscience is a burgeoning field that strives to understand the genetic, hormonal, and neural mechanisms responsible for these social structures and behaviors. Consequently, social neuroscience is highly interdisciplinary in nature and embraces the application of methods ranging from the molecular to the molar to investigate the reciprocal interactions between biological, cognitive, and social levels of analysis. The broad scope of such an endeavor introduces particular challenges associated with the integration of multiple levels of analysis. In the present mini-review, we highlight some recent findings in the field of social neuroscience and demonstrate the potential benefits of applying multilevel integrative analysis to the study of social behavior and its influence on physiology and health.

Keywords: Neuroscience; Social; Loneliness; Autonomic; Health; Multilevel.

Over countless millennia, organisms have evolved a myriad of processes that facilitate the ability to quickly evaluate situations in which they must distinguish between hostile and hospitable stimuli and select appropriate responses. In response to a particular set of environmental contingencies, a relatively small proportion of organisms has developed the ability to interact with other members of their species to form complex social structures that can facilitate the transmission of an individual's genetic information into subsequent generations by minimizing the individual likelihood of predation while maximizing access to mates and food resources (Axelrod & Hamilton, 1981). In order to successfully operate within these social networks, organisms have developed a broad array of neurobiological structures that facilitate social interactions through the rapid processing of socially relevant, species-specific information (e.g., facial expression, olfactory cues) across broad levels of the neuraxis (Adolphs, Tranel, & Damasio, 1998; Brothers, 1990; Cacioppo, Norris, Decety, Monteleone, & Nusbaum, 2009; Winslow & Insel, 2004). The field of social neuroscience seeks to understand the relationships between social behaviors and their physiological and neurobiological substrates. Importantly, the objective of such an approach represents more than the simple correlation of variables operating across individual levels of analysis. Indeed, social neuroscience is concerned with the understanding of the dynamic signaling mechanisms, be they social or physiological, which allow for the reciprocal interaction between levels of analysis. The emergent

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structures created by the collective behavior of social species, and threats to their integrity, are capable of influencing a broad range of neurobiological and physiological processes (Cacioppo et al., 2009; Cole et al., 2007; DeVries, Craft, Glasper, Neigh, & Alexander, 2007; Hawkley, Thisted, Masi, & Cacioppo, 2010b; McGowan et al., 2009; Miller et al., 2009). Indeed, various psychological, behavioral, and biological processes are locked into reciprocal causal loops (Figure 1) such that perturbations at any one level (e.g., infection) are able to reverberate across all levels (e.g., behavioral level: decreased social interaction; molecular level: elevated cytokine gene expression), which are themselves capable of feeding back into the system where the initial event occurred (e.g., increased energy stores by avoiding social threats and heightened activity of immune cells via cytokine secretion). Thus, a comprehensive scientific understanding of any species embedded within such a dynamic, social-biological circuit necessitates a multilevel, integrative perspective (Cacioppo, Berntson, Sheridan, & McClintock, 2000).

The present mini-review highlights some contemporary examples of social neuroscientific research with a particular emphasis on perspectives that integrate scientific disciplines and illustrate potential mechanisms through which social structures and processes may influence and are influenced by cellular and molecular processes. Although the field of social neuroscience has expanded rapidly, space limitations necessitate that we focus here on three primary issues. In the first section, we highlight recent work on the neuropeptide oxytocin and its role in regulating how individuals perceive their social world. In the second, we discuss some of the negative health repercussions that arise when an individual feels socially isolated. We conclude by discussing potential neurobiological messengers and pathways linking social environments and biological processes.

SOME MICROMECHANISMS OF MOLAR PROCESSES: OXYTOCIN AND THE SOCIAL BRAIN

One of the primary goals of social neuroscience is to utilize biological information to inform or constrain higher-level social psychological constructs. Through the application of biologically oriented methodologies, including imaging techniques, lesion studies, and neuropharmacological approaches, one can sometimes better identify the mechanisms underlying social psychological processes. Here we will discuss illustrative work on the neuropeptide oxytocin and how it has led to new hypotheses regarding the mechanism underlying social processes ranging from social attachment to empathy and social threat.

A quantitative relationship exists between the complexity of social groups and the relative brain size of the animals that comprise the group (Dunbar & Shultz, 2007). However, complexity does not necessarily result from increased group size; rather, the

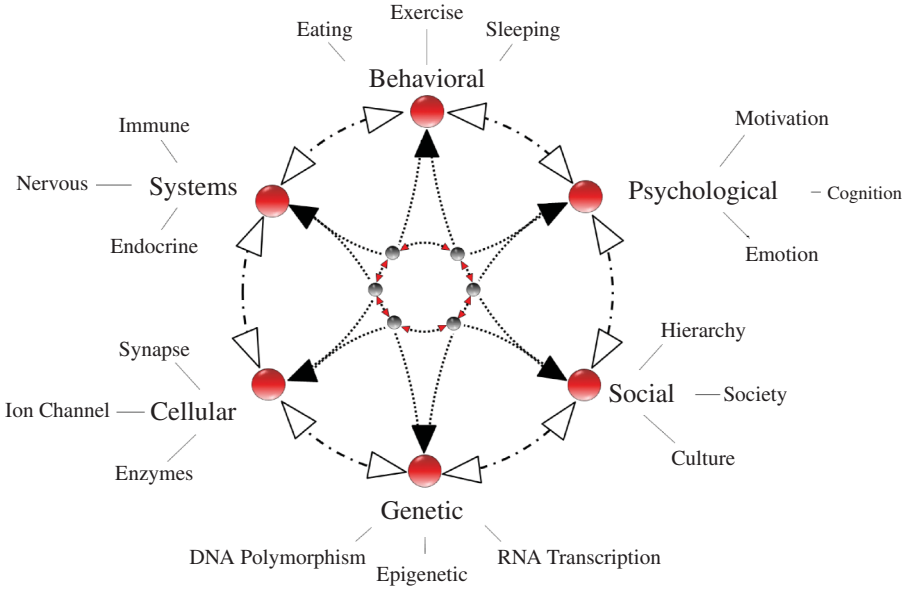

Figure 1. A reciprocal causal loop between levels of analysis.

increased complexity can derive from more elaborated individual relationships. Indeed, the association between brain size and group complexity seems to be the strongest for pair-bonding animals (Dunbar & Shultz, 2007). Over the past half-century, the hypothalamic neuropeptide oxytocin has emerged as one of the most important neurobiological substrates mediating pair bonds (Carter, 1998). For example, pharmacological and gene manipulation studies have demonstrated that oxytocin and the similar peptide vasopressin play a critical role in establishing social bonds between mates of the prairie vole through the differential expression patterns of oxytocin and vasopressin receptors within limbic structures (Ross et al., 2009; Williams, Insel, Harbaugh, & Carter, 1994). Oxytocin has also been implicated in the social behavior of various other species, including monkeys, mice, and humans (Carter, Grippo, Pournajafi-Nazarloo, Ruscio, & Porges, 2008; Heinrichs, von Dawans, & Domes, 2009; Young, 2002). Indeed, functional oxytocin signaling is necessary for social recognition within mice (Dantzer, Bluthe, Koob, & Le Moal, 1987), and central administration of oxytocin can increase social interaction between adults (Witt, Winslow, & Insel, 1992).

The manifold associations between oxytocin and social behavior in animal models have stimulated investigations of the behavioral role of this neuropeptide in humans. The oxytocinergic system has been shown to be remarkably sensitive to the neural processing of social information across both basic and psychopathological contexts in humans. For example, early parental separation has been proposed to alter central oxytocin receptor sensitivity in adults (Meinlschmidt & Heim, 2007). Further, positive social interactions lead to increased levels of oxytocin (Heinrichs, Baumgartner, Kirschbaum, & Ehlert, 2003), leading some to suggest that oxytocin mediates some of the benefits of social support in stress buffering and health (Uvnas-Moberg, 1998).

The oxytocin molecule is too large to cross the blood–brain barrier, and questions remain regarding the relative importance of peripheral oxytocin signaling and its role in central nervous system (CNS) functioning. It is therefore interesting to note that direct administration of oxytocin, whether given systemically or intranasally (ostensibly allowing some access to the CNS), appears to influence social information processes. For example, intranasal oxytocin has been shown to attenuate amygdala–brainstem coupling in response to threatening social stimuli (Kirsch et al., 2005), and intranasal delivery of oxytocin modulates the evaluation of socially relevant faces, ostensibly by differentially modulating distinct subregions of the amygdala (Gamer, Zurowski, & Büchel, 2010) and fusiform gyrus (Domes, Heinrichs, Michel, Berger, & Herpertz, 2007; Petrovic, Kalisch, Singer, & Dolan, 2008). Interestingly, the effects of oxytocin on affective processing appear to be relatively specific. For instance, oxytocin decreases emotional arousal only to threatening human stimuli; responses to generally positive and negative stimuli and to threatening animal stimuli were unaffected by oxytocin (Norman et al., 2010b) (Figure 2). In addition to diminishing the psychological and neural responses to threatening or adverse stimuli, intranasal administration of oxytocin simultaneously increases the processing of positive social information (Di Simplicio, Massey-Chase, Cowen, & Harmer, 2009; Guastella, Mitchell, & Mathews, 2008) and promotes in-group trust (De Dreu et al., 2010; Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005) while simultaneously increasing defensive aggression toward out-group members (De Dreu et al., 2010).

It must be noted that the effects of oxytocin on social affective processes are not universally positive and can vary greatly within certain populations. Indeed, intranasal oxytocin has been shown to increase empathic accuracy in individuals, but only in individuals scoring low on measures of social proficiency (Bartz et al., 2010a). Moreover, a recent study found that the effects of intranasal oxytocin on attachment representations of their mother were moderated by anxiety, less anxious individuals remembering their

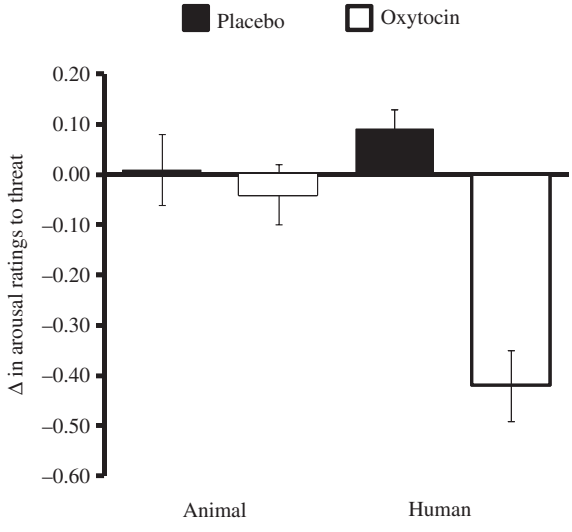

Figure 2. Oxytocin and placebo groups rated pictures from the International Affective Picture System on how emotionally arousing each slide made them feel. Oxytocin administration was found to significantly lower levels of emotional arousal to threatening slides that contained humans, but not to threatening, nonhuman-containing stimuli. Figure adapted from Norman et al. (2010b).

mother as more caring after oxytocin (vs. placebo) and more anxious individuals remembering their mother as less caring (Bartz et al., 2010b). Similarly, although oxytocin has been shown to increase trust for members of one's in-group within typical populations (De Dreu et al., 2010), it can have entirely opposite effects in individuals suffering from borderline personality disorder (Bartz et al., 2010c).

Thus, oxytocin seems to increase the salience and processing of social-approach-related cues while simultaneously decreasing social threat-related cues associated with social-avoidance behaviors. However, oxytocin is not a panacea for all social processes and can have opposite influences on psychological processes in different populations of individuals.

Taken together, the decades of research on oxytocin and its function in rodents, coupled with the recent work in humans, suggest that oxytocin plays an important role in the neurobiological mechanisms underlying social behavior and represents an important neurobiological element of the "social brain." In addition to providing a basic understanding of the human mind, the determination of the neurobiological mechanisms that allow social information to influence physiology has broad clinical relevance. Indeed, social factors, such as perceived social isolation, engender broad alterations in physiology that result in significantly higher rates of mortality, a topic discussed in further detail below.

ISOLATED BRAINS: SOCIAL NEUROSCIENCE, SOCIAL ISOLATION, AND HEALTH

One fruitful thread of research to emerge out of social neuroscience over the past two decades has been the study of the underlying mechanisms that allow social interactions to influence health. The close social connections we form with others are a primary source of the most rewarding (e.g., marriage, parenthood), as well as the most aversive (e.g., divorce, death of loved ones) experiences to which humans can be exposed. The perception that particular social needs are not being adequately met typically results in the activation of a complex set of aversive but adaptive feelings (e.g., loneliness), which serve to drive an individual to seek the fulfillment of these needs (Russell, Peplau, & Cutrona, 1980; Weiss, 1973). The absence of trusted connections with others is not only an unhappy circumstance, however; it also represents an unsafe situation (Cacioppo & Patrick, 2008). Indeed, feelings of loneliness tend to activate survival mechanisms that lead to more than transient variations in hedonic states that serve to heighten the neural sensitivity to a diverse set of threats (Cacioppo & Hawkley, 2009) Furthermore, lonely individuals display greater cognitive interference specifically for negative social words than negative, nonsocial words in a modified emotional Stroop interference task (Shintel, Cacioppo & Nusbaum, 2011), and they are more sensitive to the occurrence of pain in others than nonlonely individuals (Yamada & Decety, 2009). Furthermore, the brains of lonely individuals respond differently to social information (Cacioppo et al., 2009), and lonely individuals display stronger motivations to avoid aversive social outcomes and weaker motivations to approach good social outcomes (Cacioppo et al., 2009).

Although acute loneliness can be adaptive in the short term, chronic feelings of perceived social isolation can induce a broad range of detrimental physiological and behavioral responses that can have a rather dramatic influence on health. For example, a recent meta-analysis comprising more than 300,000 patients across 148 studies revealed that individuals who reported inadequate social relationships have a 50% greater probability of mortality as compared to patients satisfied with their social relationships (Holt-Lunstad, Smith, & Layton, 2010). Higher loneliness levels are also associated with the metabolic syndrome (Whisman, 2010), and individuals who report more frequent and recent bouts of loneliness display a significantly higher risk of cardiovascular disease and subsequent mortality (Patterson & Veenstra, 2010).

The focus in epidemiological research is on human data, a field in which the relationship between social processes and health in humans has been attributed to differences in health behaviors (House, Landis, & Umberson, 1988; Umberson & Montez, 2010). However, it appears that perceived social isolation (i.e., loneliness) influences physiological systems, including neuroendocrine, immunological, and cardiovascular processes, associated with health (Cole et al., 2007; Hawkley et al., 2010b; Norman et al., 2010a). Furthermore, the research on loneliness to date has not supported the notion that health behaviors are a sufficient cause for all adverse health outcomes. Instead, lonely individuals tend to be characterized by increases in focused catabolic processes and decreases in specific anabolic processes. For instance, lonely and nonlonely individuals spend equivalent time sleeping, but the sleep of lonely young adults is less efficacious as gauged by physiological, behavioral, and self-report measures (Cacioppo et al., 2002). Indeed, a recent study found loneliness to be associated with greater daytime dysfunction in a 3-day diary study of middle-age adults' independent demographics, health behavior, health conditions, social support, and depressive

symptoms (Hawkley, Preacher, & Cacioppo, 2010a). Moreover, cross-lagged panel analyses of the three consecutive days revealed that feelings of loneliness predicted daytime dysfunction on the subsequent day, which then was able to exert an effect on loneliness ratings the following day independently of sleep duration (Hawkley et al., 2010a). Thus, while lonely and nonlonely individuals spend similar amounts of time sleeping, the sleep is less restorative among the lonely individuals, an effect that precipitates even greater levels of perceived social isolation and is independent of social behaviors (Hawkley et al., 2010a). Furthermore, the finding that social isolation has potent influence on a broad range of physiological variables in animal models, where the potential confounding effects of health behaviors are minimized, provides further support for the postulation that the perception of social threats (e.g., isolation, rejection) and subsequent translation into neurobiological and physiological signals represent the primary means through which social information influences health. Therefore, a better understanding of the neurobiological mechanisms that allow social information to be translated into physiological processes represents an important step in the understanding of the broad range of diseases known to be altered by social factors such as loneliness.

SOCIAL CONNECTIONS AND HEALTH: SIGNAL TRANSDUCTION PATHWAYS

The correlation between social factors and health represents an important finding with obvious public health implications. Therefore, the determination of potential physiological mediators that subserve the relationship between social factors and health is a major focus of contemporary studies within the field of social neuroscience. Although various examples of this type of endeavor exist, we chose to focus upon the potential role of autonomic and neuroendocrine mediations, as this topic represents one of the faster growing areas of research within the social neuroscientific field.

Alterations in neuroendocrine and autonomic nervous system (ANS) activity represent two of the best-described mechanisms through which social signals (e.g., social isolation, social rejection) are able to modulate physiological processes (Figure 3). Higher-level corticolimbic structures (e.g., the orbitofrontal cortex, anterior cingulate cortex, and amygdala) involved in the processing of social information, including social threat, social rejection, and social cognition (Adolphs, 2009; Eisenberger, Lieberman, & Williams, 2003), also send projections to brainstem nuclei controlling both sympathetic and parasympathetic outflow (for review, see Berntson & Cacioppo, 2000; Critchley, 2005; see also Figure 4), allowing for the production of more complex patterns of physiological regulation. For example, although baroreflex responses may entail tightly regulated reciprocal patterns of autonomic control (increased sympathetic, decreased parasympathetic), the autonomic branches can change reciprocally, independently, or coactively in social-psychological contexts (e.g., social speech stress) that typically depend upon higher-level processing (Berntson, Cacioppo, Quigley, & Fabro, 1994). Therefore, individual differences in the perception of particular social challenges (e.g., social threat, perceived social isolation) are likely to result in distinct patterns of autonomic reactivity across various contexts (Newton, 2009). Indeed, lonely humans show elevated peripheral resistance (Cacioppo et al., 2002) and age-related alterations in systolic blood pressure (Hawkley, Masi, Berry, & Cacioppo, 2006), a finding that may account for some of the aforementioned associations between perceived social isolation and cardiovascular health.

SOCIAL CONNECTIONS AND HEALTH: AUTONOMIC AND NEUROENDOCRINE MECHANISMS

The relationship between social processes and ANS functioning is not limited to humans. Indeed, in cynomolgus monkeys, social instability leads to heightened activity of the sympathetic nervous system, which in turn promotes coronary atherogenesis (Manuck, Kaplan, Adams, & Clarkson, 1988). Additionally, chronic social stress in primates increases sympathetic nervous system innervation of the lymph nodes (Sloan et al., 2007), potentially leading to long-term alterations in cytokine profiles (Nance & Sanders, 2007). Socially isolated mice show more severe dysregulation of ANS functioning following cardiac arrest (Norman et al., 2010a) (Figure 3), greater ANS-mediated blood vessel growth, and tumor metastasis in cancer (Thaker et al., 2006). Similarly, social-stress-induced sympathetic activation in mice produces a broad range of effects on immune function independent of hypothalamic-pituitary-adrenal (HPA) axis function (Engler et al., 2004). Although far from an exhaustive review of the literature, the findings described above suggest that social isolation may influence mortality through the modulation of ANS activation.

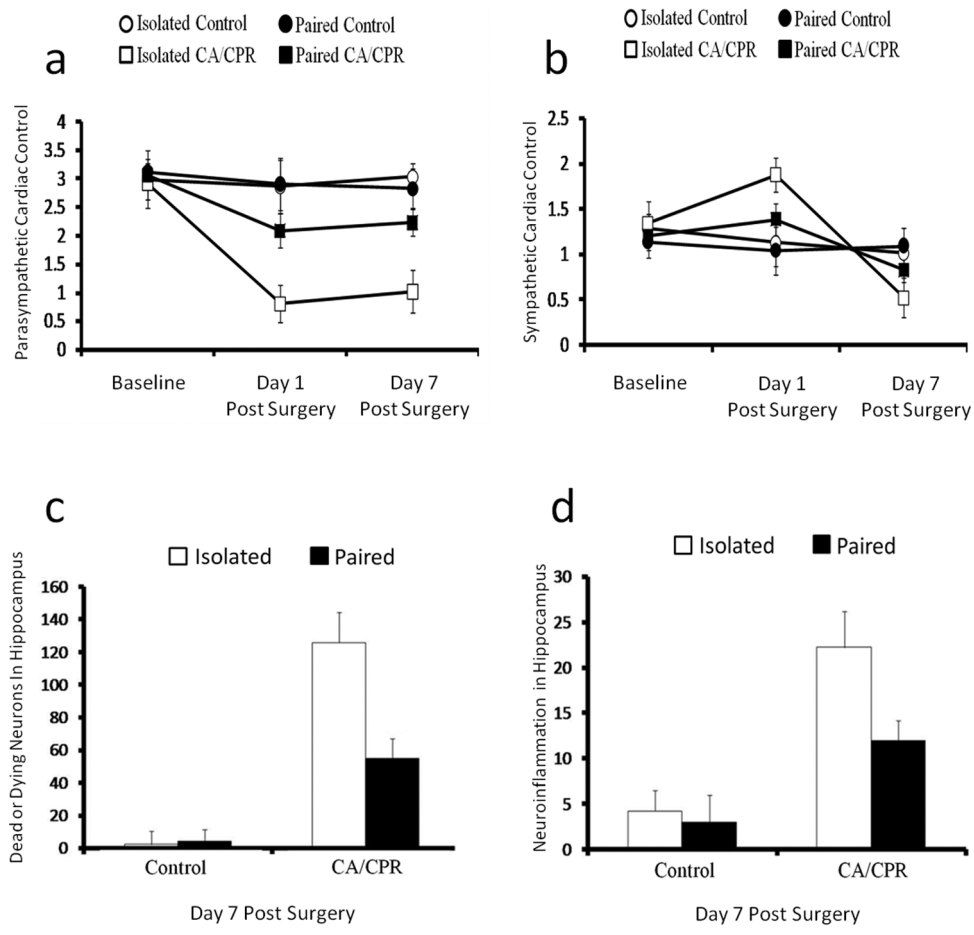

Figure 3. Animals were either socially isolated or socially housed for 2 weeks, and subjected to either cardiac arrest or control surgeries. The relative contribution of sympathetic and parasympathetic influences to cardiac autonomic control was evaluated through validated pharmacological manipulations. CA/CPR animals exposed to chronic social isolation displayed (a) significantly decreased parasympathetic cardiac control at all post-surgery time points, as well as (b) a time-dependent modulation in sympathetic cardiac control. (c) Chronic social isolation exacerbated the effect of CA/CPR on neuronal cell death and increased neuroinflammatory responses (d) within the hippocampus following surgery. Figure adapted from Norman et al. (2010a).

In addition to ANS mechanisms, social factors, including social isolation, can influence health outcomes through modulation of the HPA axis, which regulates a broad array of neuroendocrine processes involved in metabolism, reproduction, and stress reactivity (McEwen, 2005). Perceived social isolation is associated with diminished diurnal variation in HPA axis functioning (Adam, Hawkley, Kudielka, & Cacioppo, 2006; Doane & Adam, 2010) and elevated cortisol awakening responses in humans (Adam et al., 2006; Grant, Hamer, & Steptoe, 2009). Similarly, in populations of baboons, low-ranking individuals show increased basal glucocorticoid levels (Sapolsky, Alberts, & Altmann, 1997), and chronic social isolation in mice engenders broad alterations in HPA axis functioning (DeVries, Craft, Glasper, Neigh, & Alexander, 2007). Given the broad influence of glucocorticoids on immune function (McEwen & Gianaros, 2010; Sorrells, Caso, Munhoz, & Sapolsky, 2009), the dysregulation of cortisol signaling may also mediate the relationship between perceived social isolation, immune function, and health. Indeed, chronic social stress in mice has been shown to facilitate the development of glucocorticoid insensitivity in subordinate animals (Avitsur, Stark, & Sheridan, 2001), a syndrome in which immune cells become unresponsive to the typically anti-inflammatory properties of glucocorticoids. Similarly, recent data suggest that perceived social isolation in humans is associated with alterations in glucocorticoid receptor signaling that may result in a similar impairment of the physiological capacity to control inflammation by the HPA axis, despite normal circulating cortisol levels (Cole, 2008; Cole et al., 2007). Indeed, alterations in

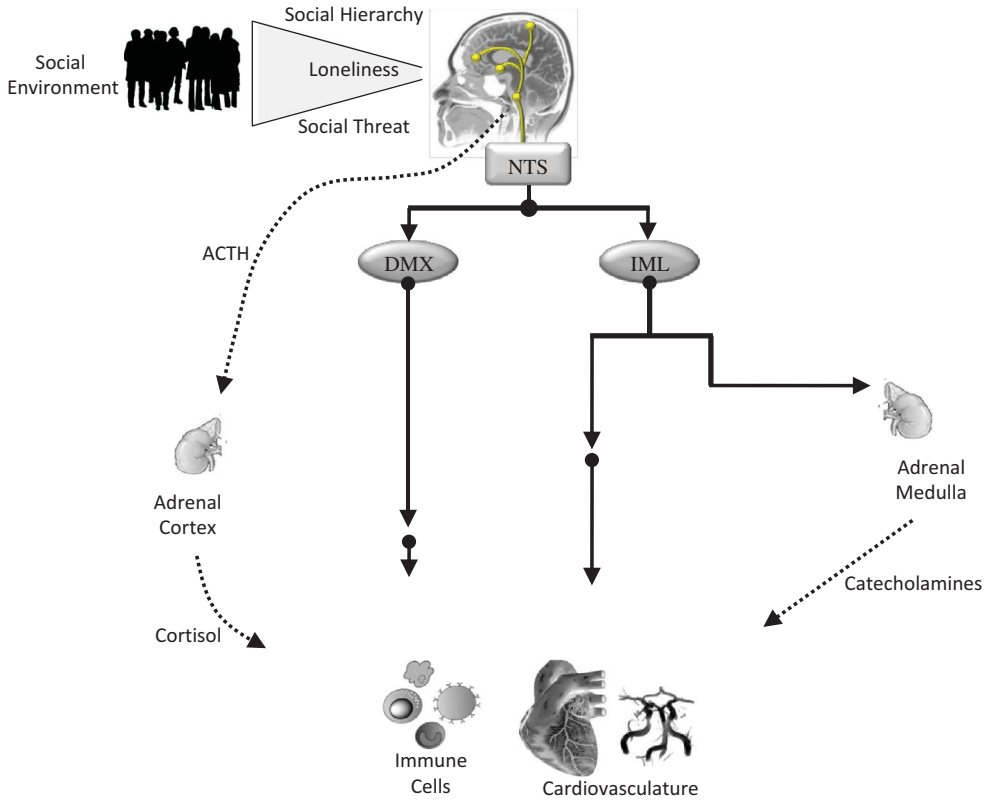

Figure 4. Top-down influences on physiological processes. Rostral brain structures process information coming in from the social environment and subsequently influence autonomic output through projections to the brainstem structures nucleus tractus solitarius (NTS) and rostral ventral medulla (Rvlm). The NTS subsequently projects to the dorsal motor nucleus of the vagus (DMX; parasympathetic control) and the Rvlm to the intermediolateral cell column (IML; sympathetic control). Sympathetic activation at the adrenal medulla results in systemic catecholamine release. Rostral brain structures influence neuroendocrine control via the hypothalamus. Activation of hypothalamic neurons via corticotropin-releasing hormone results in systemic release of adrenocorticotropic hormone (ACTH). When ACTH reaches the adrenal cortex, it induces the release of glucocorticoids. Both the autonomic and neuroendocrine systems influence the function of organs and the immune system.

glucocorticoid receptor sensitivity associated with perceived social isolation results in altered gene-expression profiles in immune cells (Cole et al., 2007; see Figure 5), a relationship which may help explain why lonely individuals show weaker immune responses and greater vulnerability to viral respiratory infections (Cohen, Doyle, Skoner, Rabin, & Gwaltney, 1997; Pressman et al., 2005). Thus, the ability of social isolation to broadly influence HPA axis functioning presents another conduit through which social information can influence health.

In addition to glucocorticoids, the HPA axis regulates a broad array of neuropeptide and steroid signaling molecules with widespread physiological and behavioral effects. As highlighted above, the HPA axis neuropeptide oxytocin is synthesized within

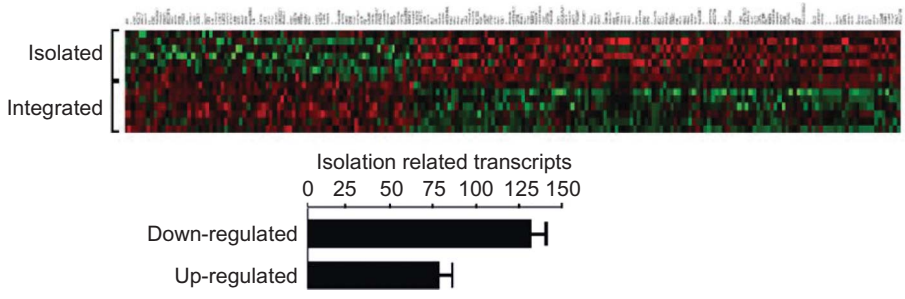

Figure 5. Differential gene expression in high- versus low-lonely individuals. High subjective social isolation is associated with a statistically significant net reduction in the number of expressed genes. Figure adapted from Cole et al. (2007).

the supraoptic and paraventricular nuclei of the hypothalamus and is in continuous interaction with various neural structures associated with the processing of social interaction through oxytocinergic neuronal projections (Carter, 1998). In conjunction with its modulation of psychological and behavioral processes, oxytocin has potent effects on physiological functioning. Indeed, as will be discussed in further detail in the next section, oxytocin has been shown to modulate health-relevant processes ranging from inflammation (Clodi et al., 2008; Iseri et al., 2005) to ischemic injury (Ondrejcakova, Ravingerova, Bakos, Pancza, & Jezova, 2009; Tugtepe et al., 2007) to atherosclerosis (Szeto et al., 2008), leading some to suggest that oxytocin may be one potential mediator of the association between social processes and health (Uvnas-Moberg, 1998).

Variations in the oxytocin system are associated with structural alterations in brain structures known to modulate autonomic and neuroendocrine functioning in humans, such as the amygdala (Inoue et al., 2010) and hypothalamus (Tost et al., 2010). Furthermore, intranasal administration of oxytocin diminishes HPA reactivity to psychosocial stress (Heinrichs, Baumgartner, Kirschbaum, & Ehlert, 2003) and elevates sympathetic and parasympathetic cardiac control (Norman et al., 2011) (Figure 6); this is a pattern of co-activation previously associated with more favorable health status. Interestingly, the influence of oxytocin on parasympathetic cardiac control was found to be dependent upon individual levels of loneliness such that elevated loneliness ratings were associated with diminished autonomic responses to oxytocin (Figure 6). This latter finding may reflect diminished oxytocin receptor activity within lonely individuals, and is consistent with previous associations between loneliness and variation in the oxytocin receptor gene (Lucht et al., 2009). Similarly, prolonged isolation from a parent during childhood is associated with diminished central sensitivity to the effects of oxytocin on HPA axis cortisol secretion (Meinlschmidt & Heim, 2007). Oxytocin also has a pronounced influence on immune function in humans. For example, the administration of the powerful immune stimulant lipopolysaccharide (LPS) typically induces large increases in circulating stress hormones and pro-inflammatory cytokines. However, simultaneous peripheral administration of oxytocin and LPS leads to diminished levels of pro-inflammatory cytokines and stress hormone levels potentially through a mechanism partially dependent on ANS functioning (Clodi et al., 2008). This body of work suggests that oxytocin dampens many of the physiological responses to stress (psychological or physiological) and is consistent with the hypothesis that diminished oxytocinergic signaling may be a contributing factor in the association between perceived social isolation on health.

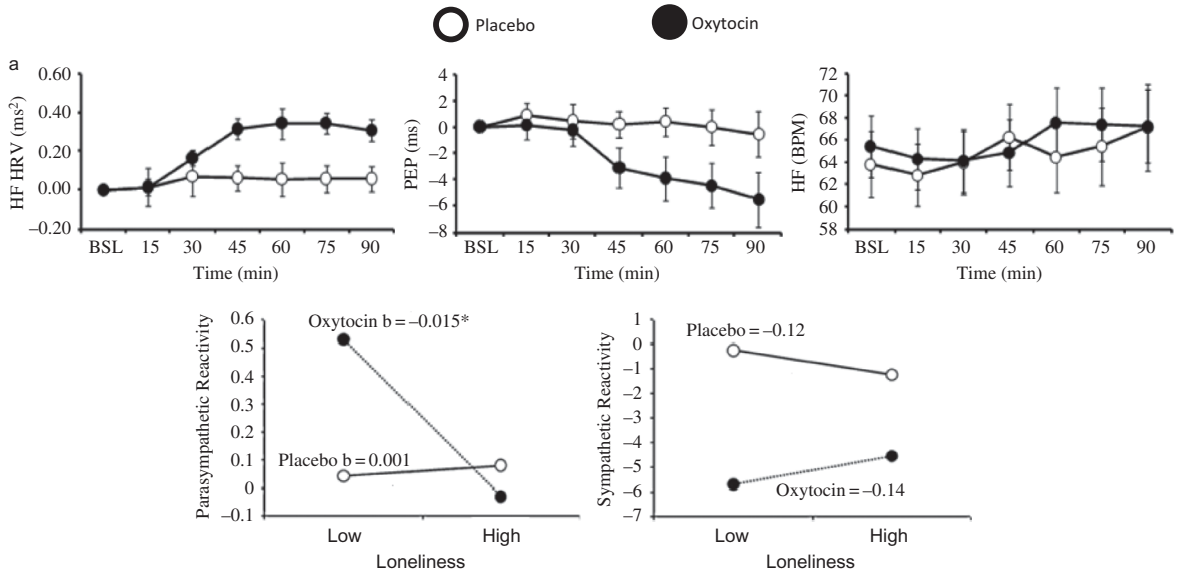

Figure 6. The influence of oxytocin on autonomic cardiac control. (a) Intranasal oxytocin administration (20 IU) significantly increased parasympathetic cardiac control as measured by high-frequency heart rate variability (HF HRV) and (b) increased sympathetic cardiac control, as measured by pre-ejection period (PEP) relative to placebo. (c) Oxytocin had no influence on heart rate. (d) The moderational effect of loneliness on cardiac autonomic reactivity to oxytocin. Elevated levels of perceived social isolation are significantly predictive of the effect of oxytocin on HF HRV change scores (t_2–t_1), with higher levels of social isolation associated with reduced sensitivity to intranasal oxytocin. HF HRV and PEP are presented as mean change from baseline ±SEM. High vs. low loneliness is presented at 1 standard deviation (*SD*) above and below the population mean. The slope of the regression line is included next to each function.

Oxytocin has been found to mitigate pathophysiological processes in various animal models of human disease. Indeed, central treatment with oxytocin reverses the effects of chronic social isolation on autonomic cardiac control and affective behavior in voles (Grippo, Trahanas, Zimmerman, Porges, & Carter, 2009). Oxytocin treatment significantly lowers blood pressure in spontaneously hypertensive male rats (Petersson & Uvnas-Moberg, 2007) and mitigates the deleterious effects of chronic social isolation on vascular oxidative stress, atherosclerosis, and adipose tissue inflammation in mice (Szeto et al., 2008). Similarly, central treatment with oxytocin reverses the effects of social isolation on depressive-like behavior and pro-inflammatory gene expression in the prefrontal cortex in neuropathic animals (Norman et al., 2010c). Conversely, pharmacological inhibition of oxytocin signaling in socially housed animals significantly increases depressive-like behavior and cytokine expression to levels seen in socially isolated animals (Norman et al., 2010c). Therefore, oxytocin is able to modulate a variety of pathophysiological processes that have been linked to social isolation, in addition to its established effects on neurobiological function and behavior.

In sum, the findings described above support the hypothesis that oxytocin may be one of the biological intermediaries that translate social information into health-relevant physiological processes such as autonomic, neuroendocrine, and immune function. Therefore, variations within endogenous oxytocin levels associated with social isolation may partially mediate the potent effects of the social environment on morbidity and mortality in humans.

CONCLUSION AND FUTURE DIRECTIONS

Knowledge regarding the brain and its associations with behavior and disease has grown exponentially during the past quarter-century. Much of the initial growth considered humans, like other social mammals, as isolated units of analysis irrespective of their particular social environment. With the development of the perspective of social neuroscience, it has become more apparent that social animals, by definition, participate in superorganismal structures and processes, and the nature of these structures and processes can have profound effects on neural, hormonal, cellular, and genetic processes as well as on cognition and behavior. For instance, recent work in animals and humans has demonstrated that the association between social isolation and health is not simply a result of changes in health behaviors, but rather of the perception of social isolation and the subsequent modulation of neural, hormonal, cellular, and genetic processes that play a role in the degradation of health and well-being. Thus, this mini-review highlights the importance of incorporating the social environment into models of various disease processes.

Like any new field, social neuroscience faces problems and challenges that must be acknowledged and addressed. For example, the complex constructs that are used in social neuroscience (e.g., empathy, trust) should not be assumed to be localizable to discrete neural or hormonal entities but rather should be decomposed into interacting subcomponents and linking mechanisms. Furthermore, the field must be careful to avoid reifying neural data per se or blindly injecting neuroscientific methods where they yield little information about biological (e.g., brain) or psychological functions. The application of methods from the neurosciences has been demonstrably helpful when used to test competing hypotheses about what these constructs, components, or computations might be. Finally, investigations are needed that use converging methods, such as neuroimaging, focal lesions, animal models, and neuropharmacological approaches. Each approach has strong limitations, but the confluence of these methods can provide more detailed information on component processes and mechanisms linking social and biological environments. In sum, the field had been built upon the foundation of multilevel integrative analysis that is capable of asking questions about all the levels of analysis underlying the mind; from genes to complex human behavior, the unprecedented growth of social neuroscience is likely to continue over the next century only if the next generation of investigation continues to increase in its theoretical, methodological, and quantitative sophistication. Neuroscientists in the twentieth century often avoided social behaviors because they were so complex. Discovering the biological mechanisms underlying social interactions is one of the major problems for the interdisciplinary field of neuroscience to address in the twenty-first century.

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