Integrative Pathways Linking Close Family Ties to Health: A Neurochemical Perspective

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Abstract

The quality of one's familial life, for better or worse, has been linked to physical health. Such associations are evident across a number of acute and chronic conditions and highlight the widespread impact that close relationships have on physical health. However, the field currently lacks a complete understanding of the integrative biological pathways underlying the association between close relationships and disease risk. This article reviews the main peripheral biological and central nervous system pathways linking positive and negative familial relationship processes to physical health outcomes. It emphasizes the role of neurochemical pathways in mediating the influence of social relationships on health-relevant peripheral physiological systems using the oxytocin system as a model. Such neurochemical approaches are an important step towards a more integrative understanding of complex biological pathways and has novel theoretical and intervention implications.

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The quality of one's close relationships has been reliably related to disease morbidity and mortality from the cradle to the grave (Cohen, 2004; Holt-Lunstad, Smith, & Layton, 2010; Uchino, 2009). In a meta-analysis of over 300,000 participants, Holt-Lunstad and colleagues (2010) found that supportive relationships were related to a 46% increased survival rate. Indeed, the link between supportive relationships and lower mortality was comparable to traditional biomedical risk factors such as diet, smoking, and exercise (Holt-Lunstad et al., 2010). Furthermore, a recent meta-analysis found that familial sources of support were more strongly linked to lower mortality compared to friendship support (Shor, Roelfs, & Yogev, 2013). There is also a smaller but growing literature on the health risks associated with negative aspects of familial relationships. Such social negativity (e.g., insensitivity, conflict) is related to increased physical health problems including earlier mortality (Brooks & Dunkel Schetter, 2011; Rook, 2015). Thus, for better or worse, close familial relationships are robust predictors of future health problems.

A crucial next step is to test and refine theoretical models linking relationships to health to facilitate translation into efficacious interventions. Understanding the complex biological mechanisms linking close relationships to health is important for both theoretical and applied reasons (Cohen, 2004). Such modeling can advance theories that make more precise predictions about the links between close ties and specific disease outcomes based on the contributing pathways. Improved knowledge of these pathways as well as the individual differences in their function is likely to lead to more theoretically grounded interventions, as well as suggest novel interventions that better target the underlying biology. For instance, social experiences and neural/ neurochemical responses in the brain reciprocally influence each other over time such

that pharmacological approaches might prove effective as an additional intervention tool (Bakermans-Kranenburg & van I Jzendoorn, 2013; Cacioppo & Cacioppo, 2015). This article thus discusses the evidence and implications of the major integrative peripheral physiological pathways linking close family relationships to health as well as outlines a model for how neurochemical pathways may mediate between them. Close family relationships are broadly defined as those characterized by frequent, strong, and enduring interdependence (e.g., long-term romantic or cohabiting relationships, immediate family members, Kelley & Thibaut, 1978). These close familial relationships are more likely to influence the long-term development and course of chronic health conditions due to their stability and importance (Uchino, 2009).

Basic Links Between Close Familial Ties and Peripheral/Central Biological Processes

Most of the existing work linking familial ties to physiology has focused on isolated peripheral biological measures that tap into autonomic, endocrine, and immune function (Uchino, 2006, see below). Altered levels of these peripheral biological measures has been directly linked to the leading causes of death worldwide including cardiovascular disease, cancer, and infectious diseases (Uchino, Smith, Holt-Lunstad, Campo, & Reblin, 2007).

The autonomic nervous system is divided into the sympathetic and parasympathetic nervous systems (SNS, PNS). Observational work suggests that social support from close others predicts lower catecholamine (CAT) levels, which reflects less SNS activity (Grewen, Girdler, Amico, & Light, 2005). That is, familial social support has been linked to lower urinary CATs, whereas familial strain has been related to higher CATs (Seeman, Gruenewald, Cohen, Williams, & Matthews, 2014). In terms of the PNS, studies have utilized respiratory sinus arrhythmia (RSA) as an index. RSA is the rhythmical fluctuations in heart periods occurring at the respiration band (i.e., .12 - .40 Hz, Berntson, Cacioppo, & Grossman, 2007). General models in

the area highlight the potential role of the PNS in social engagement and self-regulatory processes important to close relationships (Porges, 2007; Thayer, Hansen, Saus-Rose, & Johnsen, 2009). More specific conceptual models suggest that (a) positive emotions, social functioning, and tonic RSA reciprocally influence each other over time (Kok et al., 2013) and (b) alterations in RSA reflect a depletion of self-regulatory resources linked to close ties (e.g., conflict) that may compromise health (Smith et al., 2011).

Cardiovascular activity is one important health-relevant outcome that is regulated by the SNS and PNS. Consistent with the research reviewed above, parent-adolescent dyads and married couples that engage in more positive relationship interactions show dampened cardiovascular reactivity compared to more negative relationship interactions (Manczak, McLean, McAdams, & Chen, 2015; Nealey-Moore, Smith, Uchino, Hawkins, Olson-Cerny, 2007). Higher marital quality is also associated with lower cardiovascular reactivity during lab-based conflict discussions (Robles, Slatcher, Trombello, & McGinn, 2014). Similar findings are evident in studies examining family relationship processes on ambulatory blood pressure (ABP) during daily life (Stadler, Snyder, Horn, Shrout, & Bolger, 2012). For instance, higher marital quality as well as interventions aimed to improve marital function are linked to lower ABP (Holt-Lunstad, Birmingham, & Light, 2008; Stadler et al., 2012).

Another component of the response to stress affected by close family relationships is activation of the hypothalamic-pituitary-adrenal (HPA) axis that culminates in the release of cortisol. Cortisol is an important endocrine hormone that has broad biological influences including increased glucose metabolism/lipolysis and inhibition of immune processes (Sapolsky, Romero, & Munck, 2000). Studies suggest that close family relationships affect cortisol levels in both laboratory settings and daily life. In laboratory studies, lower maternal sensitivity and

mother-child separation are related to increases in infant cortisol level and delays in recovery (Hostinar, Sullivan, & Gunnar, 2014). In addition, familial processes in everyday life (e.g., intimacy) are linked to more favorable cortisol profiles (Ditzen, Hoppmann, & Klumb, 2008; Stadler et al., 2012). However, a recent meta-analysis did not find marital quality to predict cortisol levels (Robles et al., 2014). There was significant variability but too few studies to conduct a formal analysis so more work will be needed to determine potential moderators of the connection between marital quality and cortisol levels.

The quality of close familial relationships has also been linked to immune system function, which is the body's main defense against infectious and malignant diseases (Uchino, Vaughn, Carlisle, & Birmingham, 2012). The biological significance of these associations is evident as higher marital satisfaction is associated with a stronger antibody response to vaccination and increased marital conflict is related to slower wound healing (Kiecolt-Glaser et al., 2005; Phillips et al., 2006). One of the most active recent areas of research is on inflammation, which is the immune system response to infection and injury. While local/short-term inflammation is typically beneficial in processes such as wound healing, systemic/long-term inflammation (e.g., C-reactive protein, IL-6) is related to health problems such as diabetes, cardiovascular disease, and some cancers (Kiecolt-Glaser, Gouin, & Hantsoo, 2010). Importantly, the perception of supportive family relationships is related to lower inflammation, whereas negativity in family relationships results in acute increases in inflammation (Kiecolt-Glaser et al., 2005; Yang et al., 2014).

Each of these peripheral physiological systems are regulated by brain structures that are also integral for responding to social stressors and rewards (Eisenberger, 2013; Lieberman, 2007). Therefore, structures such as the cingulate and insular cortices are important mediators of

social stressors on peripheral physiology. Not surprisingly, social support appears to act in these areas to reduce peripheral effects of social stressors (e.g. Eisenberger, Taylor, Gable, Hilmert, & Lieberman, 2007). In addition, positive experiences with close others are not only associated with decreased activity in these regions (e.g., cingulate) but also associated with increased activity in "reward" brain regions such as the ventral striatum, septal area, and ventral tegmental area (Cacioppo, Bianchi-Demicheli, Hatfield, & Rapson, 2012; Inagaki & Eisenberger, 2012). Reward-related stimuli that activate these areas can in some cases reduce stress-related neuroendocrine responses (Creswell, Pacilio, Denson, & Satyshur, 2013). Coan and colleagues (2006) found that holding a spouse's hand during stress was associated with attenuated threat-related responses in the insula and hypothalamus, areas that influence the aforementioned peripheral physiological pathways. Moreover, marital satisfaction scores were directly correlated with lower threat-related neural activation in these areas while holding the spouse's hand.

The Neurochemistry of Close Relationships: Oxytocin as a Model System

A persistent and critical challenge for the field has been determining how these robust associations between close ties and disease-relevant peripheral physiology are instantiated. In other words, what interactional processes are involved in converting ongoing social interactions into a cascade of enduring physiological signatures that affect health? One important class of models centers around the notion of coregulation which involves the coordination of gaze, speech, and movements between individuals that serve to strengthen (or weaken) the bond between them (Semin & Cacioppo, 2008). Importantly, this coordination of interpersonal processes is also reflected in each individual's underlying physiological activity. This interweaving of physiology between individuals serves as a springboard for multiple models and has been variously termed coregulation, synchrony, attunement, social baseline, or interpersonal

emotion regulation (e.g., Sbarra & Hazan, 2008). Although there are differences between models (Hove & Risen, 2009; Sbarra & Hazan, 2008), these general processes appear important for the development and maintenance of close relationships and may be key contributors to physiology and health.

In the following section, these theories are extended by focusing on how coregulation may occur at a neurochemical level and how this may impact the regulation of the aforementioned peripheral physiological systems that influence disease. Multiple neurochemical systems in the brain influence the regulation of peripheral physiology and are likely to mediate social influences on health. However, due to space constraints the focus is on the oxytocin system because it has the largest evidence base. To orient the reader, a brief introduction to the anatomy of the oxytocin system is provided (see supplementary information for greater detail). Oxytocin neurons reside in the hypothalamus and because forebrain inputs synapse in limbic (e.g. lateral septum, medial amygdala) or hypothalamic nuclei before signaling oxytocin neurons, social information that reaches oxytocin neurons is likely to be highly processed and elaborated. Once activated, oxytocin neurons can signal in several different ways. One is via axonal projections to the pituitary that release oxytocin into the bloodstream to act as a hormone by binding to receptors on cells. Another is via projections from the hypothalamus to many forebrain regions including the ventral striatum and amygdala as well as the cingulate, insular, and association cortices (Knobloch et al., 2012) where oxytocin can signal in a more targeted fashion on the oxytocin receptors located in these areas. The degree to which release between these forebrain and pituitary projections is coordinated depends on the stimulus and context, with some situations eliciting coordinated release and others not (Neumann, 2007).

Oxytocin and Coregulation

A major reason to focus on the oxytocin system is that there is evidence in both human and animal models that interacting with one's partner or offspring can impact one's oxytocin transmission and that changes in oxytocin transmission can promote behaviors that facilitate further bonding. Thus, oxytocin signaling may be an important nexus in a positive feedback loop of reciprocal coregulation. Because of oxytocinergic influences on the HPA axis, immune system, and autonomic nervous system, this coregulation of oxytocin is poised to have physiological effects that impact health. This model of neurochemically mediated coregulation and health is depicted schematically in Figure 1 and discussed in greater detail below. The evidence reviewed below should be considered in light of general methodological concerns regarding this area and the field more generally (see online supplementary information). Nevertheless, when the animal and human literature on oxytocin, stress, and social interaction is viewed as a whole there is an emerging picture supportive of the model in Figure 1. Although not a focus of this paper, the model is generally consistent with psychological models which suggest that relationship threats (e.g., negativity; Taylor, Saphire-Bernstein, & Seeman, 2010) or closeness (e.g., positivity; Carter, 2014) can modulate oxytocin release and that elevations in oxytocin can increase social salience (Shamay-Tsoory & Abu-Akel, 2016), approach (Kemp & Guastella, 2011), or affiliative motivation depending on the context (Bartz, 2016). The critical emphasis here is that neurochemical signaling is not just an intrapersonal process, but also an interpersonal one. Below, evidence is reviewed in support of the model by focusing on studies of closely bonded individuals for whom affiliation is a salient goal. As discussed later, the effects of oxytocin may be very different in other contexts.

Insert Figure 1 here

The first step in identifying oxytocin's role in coregulation is demonstrating that social interactions influence oxytocin signaling. This evidence is based on inferences from peripheral measures of oxytocin. For example, the duration of gaze at an infant by a mother during a structured laboratory interaction is related to her increase in extracted plasma oxytocin (Kim, Fonagy, Koos, Dorsett, & Strathearn, 2014). During a structured interaction with their infant, the more affectionate touch the mother displayed or the more stimulatory touch (e.g. prodding to induce play) the father showed, the greater the increase in unextracted plasma and salivary oxytocin in the parent (Feldman, Gordon, Schneiderman, Weisman, & Zagoory-Sharon, 2010). These effects can also be seen at the neural level. A mother's increase in plasma oxytocin (extracted) when interacting with her infant is correlated with neural activation in the ventral striatum and hypothalamus when looking at images of her infant relative to other infants (Strathearn, Fonagy, Amico, & Montague, 2009). The ventral striatum is a critical region for reward and these results suggest that gazing at their infant is more rewarding for mothers whose oxytocin levels show the largest response to gazing at their infant. Furthermore, hearing comforting and reassuring words from one's mother by phone after a stressor increases urinary oxytocin relative to a comforting conversation via instant message (Seltzer, Prososki, Ziegler, & Pollak, 2012) or no interaction (Seltzer, Ziegler, & Pollak, 2010).

A second element of coregulation is that oxytocin appears to increase behaviors facilitating social engagement. When receiving intranasal oxytocin, fathers show greater stimulation of their toddler's exploration during a play session in the laboratory compared to placebo (Naber, van Ijzendoorn, Deschamps, van Engeland, & Bakermans-Kranenburg, 2010). Similarly, when fathers receive intranasal oxytocin they show greater touching behavior (index

of affectionate and stimulatory touch) compared to placebo (Weisman, Zagoory-Sharon, & Feldman, 2012).

Especially intriguing is that these oxytocin induced behavioral changes can influence oxytocin levels in the interaction partner, suggesting that coregulation can be a dyadic process. In the aforementioned study, when the father receives intranasal oxytocin the interaction with his infant triggers a larger increase in the infant's unextracted salivary oxytocin than when the father receives placebo. Furthermore, these changes are associated with increased tonic RSA in both the father and the infant, thereby affecting peripheral measures of health in both individuals. This mutual coordination of peripheral oxytocin (extracted) and tonic RSA has even been seen between humans and their pet when intranasal oxytocin was given to the dog (Nagasawa et al., 2015; Romero, Nagasawa, Mogi, Hasegawa, & Kikusui, 2014). The intranasal oxytocin facilitated the dog's gaze with their owner, which lead to corresponding increases in urinary oxytocin in the owner as well as the dog. These intriguing findings demonstrate how two bonded individuals can mutually influence each other's physiology in a salubrious manner.

There is some evidence that coregulation of oxytocin is occurring in romantic relationships as well. For example, in an initial study of male subjects and a replication, participants rated their partners as more attractive when receiving intranasal oxytocin than when receiving placebo. In both studies, oxytocin increased activity in the ventral striatum to viewing their partner's face relative to an unfamiliar woman's face, suggesting that oxytocin enhanced the reward value of their partner (Scheele et al., 2013). In another study, plasma oxytocin (unextracted) was higher in new lovers than individuals not in a relationship and was correlated with an index of behavioral and affective reciprocity recorded during a conversation about a shared positive experience (Schneiderman, Zagoory-Sharon, Leckman, & Feldman, 2012).

Similarly, expression of affiliative cues while recounting an experience of love was also associated with an increase in unextracted plasma oxytocin (Gonzaga, Turner, Keltner, Campos, & Altemus, 2006). It should be noted an association between positive social interactions with close others and increases in peripheral measures of oxytocin has not been universally found (Ditzen et al., 2007; Gouin et al., 2010; Smith et al., 2012), which could reflect methodological reasons at either the biological (e.g. oxytocin assay differences) or psychological (e.g., context, Bartz, Zaki, Bolger, & Ochsner, 2011) levels.

Oxytocin effects on Disease Relevant Peripheral Physiological Systems

A key component of the model (Figure 1) is that shifts in oxytocin levels can have direct effects on the peripheral physiological systems impacting health as shown by prior studies on familial positivity/negativity and the autonomic, neuroendocrine, and immune systems. One system directly influenced by oxytocin is the HPA axis. The neurons in the hypothalamus that initiate the HPA response express the receptor for oxytocin (Neumann, Wigger, Torner, Holsboer, & Landgraf, 2000). When oxytocin binds to this receptor, it inhibits HPA axis activation and thus cortisol release. The inhibitory effect of oxytocin on stress-induced cortisol release is also enhanced by social support from close others (Heinrichs, Baumgartner, Kirschbaum, & Ehlert, 2003). In other words, social support and oxytocin act synergistically to dampen stress reactivity. Oxytocin can also act in brain stem areas controlling vagal output (Higa, Mori, Viana, Morris, & Michelini, 2002). Accordingly, intranasal administration of oxytocin elicits an increase in RSA (Norman et al., 2011), which is associated with social engagement and improved self-regulatory capabilities. Although less studied in terms of close relationship processes, there is also evidence that oxytocin can decrease blood pressure

(Gutkowska & Jankowski, 2012); relationship interventions that increase oxytocin also decrease blood pressure (Holt-Lunstad et al., 2008).

There has been less extensive investigation of oxytocin's effects on inflammation, though there is good reason to expect it to be involved with familial influences on inflammation as well. Experimental stimulation of the immune system with a bacterial challenge (endotoxin administration) induces a robust increase in proinflammatory cytokines as well as feelings of social disconnection (Eisenberger, Inagaki, Mashal, & Irwin, 2010). The increase in cytokines after bacterial challenge is reduced by peripheral administration of oxytocin (Clodi et al., 2008). The specific pathways responsible for these anti-inflammatory effects are being investigated in ongoing work but one possibility is that oxytocin is acting centrally on brainstem nuclei controlling the vagus nerve to suppress peripheral production of inflammatory cytokines (Higa et al., 2002; Tracey, 2007). Thus, oxytocin can impact multiple health-relevant physiological pathways and is ideally positioned to bridge the social realm and the biological systems that contribute to disease.

Findings in animal models corroborate and extend the human results reported here. In rodent models, administration of oxytocin prevents the negative effects of social isolation on the cortisol response to stress (Detillion, Craft, Glasper, Prendergast, & DeVries, 2004), neuro-inflammation (Karelina et al., 2011), and vagal tone (Grippo, Trahanas, Zimmerman, Porges, & Carter, 2009). Conversely, blockade of central oxytocin receptors, which cannot be done in humans, prevents the positive effects of social housing on each of these peripheral physiological measures. The consistency of these data across both human and animal models (which afford greater control) strongly suggest that oxytocin mediates a portion of the social effects on health (Taylor et al., 2000). Importantly, animal models show that oxytocin has protective effects on

diverse health conditions such as myocardial infarction, hypertension, and obesity (Blevins & Baskin, 2015; Jameson et al., 2016; Moghimian et al., 2013). However, direct evidence for oxytocin's protective role in human disease outcomes is virtually nonexistent and should be a priority of future research on the model.

The model in Figure 1 also suggests that health problems can ultimately develop when individuals have insufficient social contact. Parental neglect of a child is a well-documented risk factor for poor relationship as well as health outcomes in adulthood. Thus, infants and children who receive less attuned parenting will experience less of an increase in oxytocin during this critical period of brain development, which might have enduring effects on the function of their oxytocin system and its influence on the mechanistic central and peripheral pathways detailed earlier. Consistent with this, women who suffered childhood abuse have lower cerebrospinal fluid oxytocin concentrations in adulthood (Heim et al., 2009). Similarly, men who experienced early life stress have lower unextracted plasma concentrations of oxytocin (Opacka-Juffry & Mohiyeddini, 2012). That early life stress alters the oxytocin system is further supported by studies administering oxytocin (see Bakermans-Kranenburg & van I Jzendoorn, 2013 for a review). For example, individuals who grew up with a mother who frequently withdrew her love showed less altruistic behavior after oxytocin administration when adults (Riem, Bakermans-Kranenburg, Huffmeijer, & van Ijzendoorn, 2013). Such preliminary data are consistent with a life history strategy of reduced investment in social bonds and relationships triggered by experiences of early life stress (Del Giudice, Ellis, & Shirtcliff, 2011).

Future Directions and Conclusions

The existing work on neurochemical models involved in the pathways from close social relationships to health holds much promise. However, there are several issues that will require

additional attention. One issue is the need to elucidate the role of genetic variation in the oxytocin system. In light of the methodological challenges associated with measuring oxytocin or administering it intranasally (see supplemental material), genetic approaches have the potential to provide convergent evidence for the role of oxytocin in connecting familial relationships with health. Animal models suggest that such variation can have robust effects on social bonding (King, Walum, Inoue, Eyrich, & Young, 2015), but this potential has not been realized yet in humans, as associations between variation in oxytocin receptor genes and behavior have not been particularly robust (Bakermans-Kranenburg & van Ijzendoorn, 2014). There are multiple reasons for the lack of consistency, but one is that the most studied genetic variants within the oxytocin gene or the oxytocin receptor gene (*OXTR*) do not have clearly defined effects on cellular function. Alternative approaches to be taken in the future are to look at variants in the *OXTR* that have demonstrated cellular-level functional effects (Myers et al., 2014), variants in other genes that are involved in oxytocin signaling (e.g. *CD38,* Algoe & Way, 2014), or epigenetic marks affecting oxytocin (Haas et al., 2016) or oxytocin receptor expression (Gregory et al., 2009). These approaches will provide greater opportunity to investigate the effects of the oxytocin system outside of the laboratory. With increasing evidence that epigenetic marks in peripheral tissue can be correlated with central ones (Turecki & Meaney, 2016), it will be possible to examine how familial experiences elicit epigenetic changes that lead to enduring changes in the expression of genes within the oxytocin system. Likewise, as additional functional oxytocinergic gene variants become identified it will be possible to examine how they moderate familial experiences.

Oxytocin is also just one of a cocktail of neurochemicals that are likely involved in social influences on health. For example, there is increasing evidence for the opioid system mediating

social influences on health in a manner similar to the oxytocin system (Way, 2013). In multiple species, blockade of the primary opioid receptor prevents the formation of bonds between mothers and infants (Shayit, Nowak, Keller, & Weller, 2003) as well as partners (Resendez et al., 2013). Social sadness leads to reductions in endogenous opioid signaling (Zubieta et al., 2003). Similarly, blockade of endogenous opioid signaling reduces daily reports of feeling socially connected with close others (Inagaki, Ray, Irwin, Way, & Eisenberger, 2016). These psychological effects are likely to have important peripheral physiological effects as well. For example, the endogenous opioids are powerful regulators of peripheral physiological systems such as the HPA axis (Wuarin & Dudek, 1996). An important area for future research will be delineating the relative and interactive role of the oxytocin, opioid, and other neurochemical systems in mediating social influences on health.

In light of the number of clinical trials testing intranasal oxytocin administration for mental health disorders (Wudarczyk, Earp, Guastella, & Savulescu, 2013), the question arises as to whether it could be used to improve relationships and subsequent physical health. This is unlikely to be a simple panacea. Although the focus of this review is on closely bonded individuals, there are multiple examples of how intranasal oxytocin can have different effects depending the nature of the person one is interacting with (Bartz et al., 2011). For instance, intranasal oxytocin increases in-group trust but has more complex (non-significant) influences on out-group distrust (see meta-analysis by van Ijzendoorn & Bakermans-Kranenburg, 2012). Familial ties also differ in their underlying positivity and negativity so it is unclear to what extent such an approach would facilitate strictly positive interactions (Uchino, Smith, & Berg, 2014). A final therapeutic challenge is that oxytocin is less likely to help those who need it the most. As

described above, those experiencing early adversity are less responsive to intranasal oxytocin as are those who are lonely (Norman et al., 2011).

Based on the studies indicating that intranasal oxytocin interacts synergistically with social support behaviors (Heinrichs et al., 2003), it is postulated that if oxytocin is to be used successfully in therapy to improve health, it is likely to have the most positive effects by being combined with interventions that involve a social component. Oxytocin might thus be combined with empirically-supported interventions (e.g., functional family therapy, Alexander, Waldron, Robbins, & Neeb, 2013), as well as more recent relationship interventions such as meditation (e.g., loving-kindness meditation, Isgett, Algoe, Boulton, & Way, in press), dyadic approaches (e.g., marital, Sher et al., 2014), and more general family-based primary prevention efforts (Repetti, Robles, & Reynolds, 2011). In an intriguing study, Johnson and colleagues (2013) found that emotionally focused therapy, which attempts to strengthen attachment bonds, lowered threat-related neural activity in distressed couples. These changes were particularly pronounced in couples who were lower in marital quality to begin with. Of course, primary prevention efforts are likely to have the biggest long-term payoff and one recent intervention found that training families in parenting skills was related to lower levels of inflammation in the child approximately 8 years later (Miller, Brody, Yu, & Chen, 2014). A novel future research agenda would thus be to examine if integrating such relationship interventions with neurochemical approaches would provide further benefits. For example, optimizing these psychosocial or behavioral interventions to maximize drug response or using epigenetic information to target therapy.

In conclusion, the more immediate benefit of studies of oxytocin, and, the neurochemical approach more generally, is to facilitate theoretical understanding of the mechanisms by which

close ties impact health. Carefully integrating psychological and biological approaches will be critical for a complete understanding of social influences on health as evidenced by the last decade of oxytocin research. Were oxytocin studied without attention to the psychological context, it would be viewed as having inconsistent or non-reproducible effects: increasing a particular behavior in one study and decreasing it in another. However, when one considers the psychological context (e.g., the nature of one's relationship to the interaction partner) a more coherent picture emerges. Thus, psychologists and neuroscientists have much to learn from each other and it is hoped that the coming decade witnesses increased interdisciplinary dialogue that aides in the ultimate goal of utilizing integrative theories to promote physical health outcomes.

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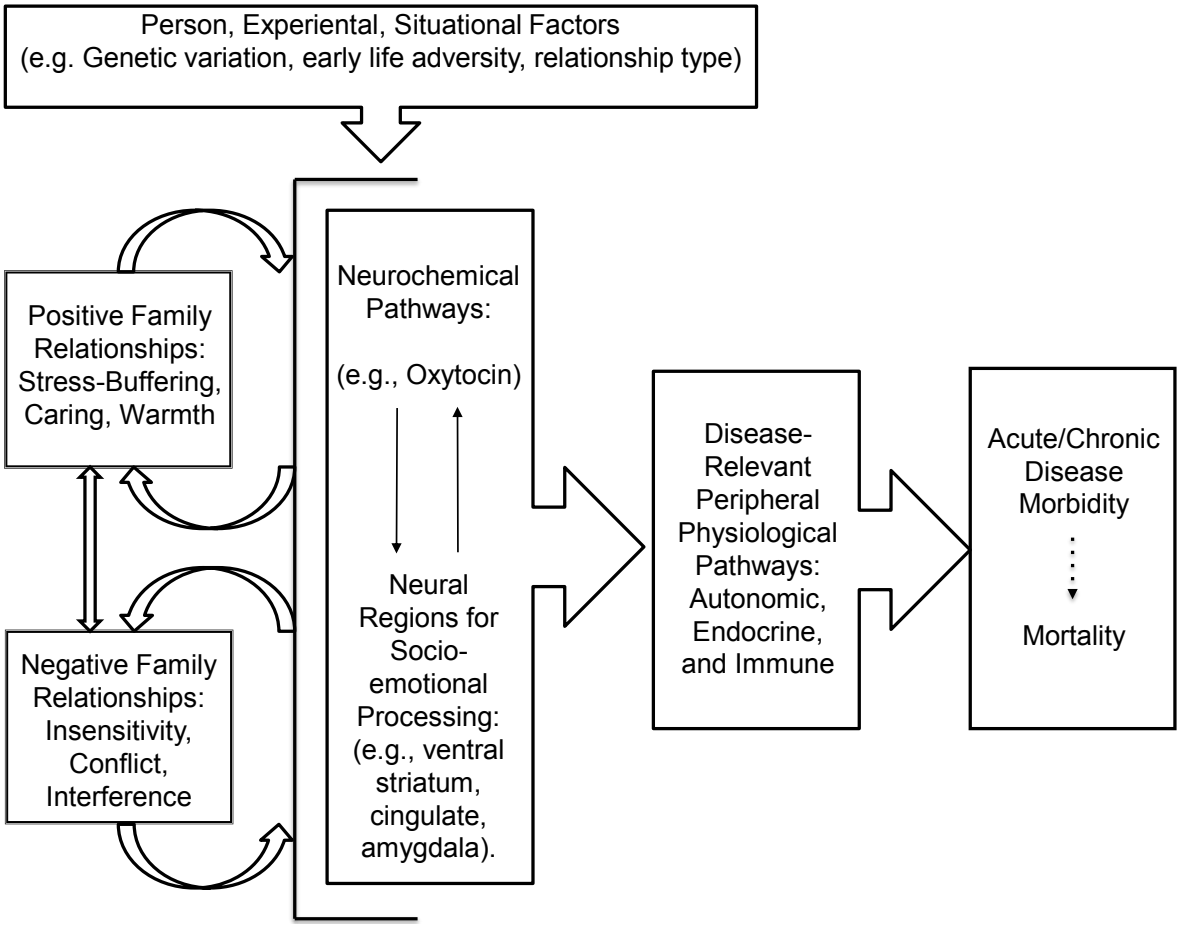

Figure 1. General neurochemical model linking positive and negative aspects of close relationships to health outcomes.