Connecting Prosocial Behavior to Improved Physical Health:
Contributions from the Neurobiology of Parenting

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Author Note

This research was supported by the National Science Foundation grant BCS 0820609 to SLB. The authors thank Michael Numan, Stephanie Preston, and Dylan Smith for feedback on earlier drafts of the manuscript.

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Abstract

Although a growing body of evidence suggests that giving to (helping) others is linked reliably to better health and longevity for the helper, little is known about causal mechanisms. In the present paper we use a recently developed model of caregiving motivation to identify possible neurophysiological mechanisms. The model describes a mammalian neurohormonal system that evolved to regulate maternal care, but over time may have been recruited to support a wide variety of helping behaviors in humans and other social animals. According to the model, perception of need or distress in others activates caregiving motivation, which in turn, can facilitate helping behavior.

Motivational regulation is governed by the medial preoptic area of the hypothalamus, interacting with certain other brain regions, hormones, and neuromodulators (especially oxytocin and progesterone). Consideration of neurohormonal circuitry and related evidence raises the possibility that it is these hormones, known to have stress-buffering and restorative properties, that are responsible, at least in part, for health and longevity benefits associated with helping others.

Keywords: altruism, helping, caregiving, health, bonding, evolution, prosocial behavior, oxytocin, progesterone, neuroscience, neuropeptide, stress

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The human tendency to help others in need—prosocial behavior¹—has received a great deal of attention from psychologists, biologists, economists, and sociologists. We know, for example, that prosocial behavior is ubiquitous (Rossi, 2001), and that it can be evolutionarily adaptive, particularly when it is reciprocated directly or indirectly (Alexander, 1987; Hamilton, 1972; Nowak and Sigmund, 1998), enables the helper to avoid punishment (e.g., Fehr and Fischbacher, 2003), enhances the helper's reputation and mating success (e.g., Zahavi, 1995; Zahavi, Zahavi, Balaban, & Ely, 1999), or is directed at related (Hamilton, 1964) or interdependent individuals (S. L. Brown & Brown, 2006; Roberts, 2005; Tomasello, Melis, Tennie, Wyman, & Herrmann, 2012). Debates continue over the psychological motivation for prosocial behavior (e.g., selfish vs. selfless, Batson, 1998; Batson, Turk, Shaw, & Klein, 1995; Cialdini, Brown, Lewis, Luce, & Neuberg, 1997), but research generally documents that psychological and physical benefits accrue to helpers.

Social psychological studies demonstrate that prosocial behavior can elevate the helper's mood (e.g. Yinon & Landau, 1987) and is associated with relief from negative states such as sadness, distress, and guilt (Cialdini, et al., 1997), and improvements in relationship satisfaction (Brunstein, Dangelmayer, & Schultheiss, 1996). Moreover, recent evidence suggests that providing help may be a more powerful predictor of physical and mental health than receiving help from others (e.g.S. L. Brown, Brown, House, & Smith, 2008; S. L. Brown, Nesse, Vinokur, & Smith, 2003;W. M. Brown, Consedine, & Magai, 2005; Schwartz, Meisenhelder, Ma, & Reed, 2003). For example,

giving, but not receiving social support, was shown to be associated with improved well-being (Schwartz et al. 2003), reduced morbidity (Avlund, Damsgaard, & Holstein, 1998; W. M. Brown, et al., 2005; Hays, Saunders, Flint, Kaplan, & Blazer, 1997), recovery from spousal loss (S. L. Brown, et al., 2008), and longevity (S. L. Brown, et al., 2003). Importantly, associations of helping behavior with mortality risk and bereavement have been demonstrated using longitudinal designs, and after controlling (statistically) for a variety of possible confounds including demographics, social integration and contact, baseline helping, self-rated health, functional limitations, health behaviors, mental health, interviewer ratings of health, personality traits, and other relationship factors such as dependence or equity. Together this research suggests that links between helping behavior and physical health cannot easily be attributed to a “helping personality,” or to the tendency for healthier individuals to help others (S. L. Brown, et al., 2003; S. L. Brown, et al., 2009a ; Roth, et al., 2013).

Of course, helping others has not always been viewed as beneficial to the helper. Consider data from many studies of informal caregiving, which suggest that helping family members and loved ones in need produces caregiver distress—psychological burden and compromised health (Schulz, O’Brien, Bookwala, & Fleissner, 1995; Vitaliano, Zhang, & Scanlan, 2003), and even mortality (Schulz & Beach, 1999). Although this negative appraisal of informal caregiving has been pervasive in the informal caregiving literature, most supportive studies are plagued by a host of research design limitations, including reliance on convenience samples, lack of appropriate controls, failure to assess caregiver outcomes longitudinally, and confounds between helping behavior and other, potentially stressful aspects of the caregiving situation.² The

majority of “caregiver stress” studies, for example, fail to distinguish between the presumed stress associated with helping *behavior* (e.g., assisting someone with activities of daily living) and stress associated with *feelings* about the recipient (e.g., the sense of grief, sadness, or loss of loving someone who is dying; for a critical review, see R. M. Brown & Brown, 2014). Methodological difficulties notwithstanding, and despite meta-analyses showing inconsistent, or no adverse health effects uniquely attributable to informal caregiving (Pinquart & Sorenson, 2003, 2007), mainstream health research and public policy opinion regarding informal caregiving seem decidedly negative (R. M. Brown & Brown, 2014).

More recent evidence from better-controlled, large-scale prospective studies suggests that even informal caregivers experience positive states associated with helping others, including improvements in psychological well-being, health, and longevity (; S. L. Brown, et al., 2009a; Fredman, et al., 2010; O’Reilly, et al., 2008; Poulin et al., 2010; Roth, et al., 2013). It should be noted that the caregiver longevity advantage holds even when hours invested in caregiving are relatively high. In those studies reporting hours spent caregiving, the caregiver longevity advantage was significant at > 14 hours per week in Brown, et al. (2009a), and at ≥ 50 hours per week in O’Reilly, et al. (2008); there was a nonsignificant ($p < .08$) trend in the direction of a caregiver longevity advantage at > 14 hours per week in Roth, et al. (2013). These findings are consistent with mounting evidence from studies of volunteering demonstrating that volunteers (a) have better health than non-volunteers (for a recent narrative review, see von Bonsdorff & Rantanen, 2011), (b) exhibit a slower decline in self-reported health and functioning levels than non-volunteers (Lum & Lightfoot, 2005), and (c) have a lower risk of

mortality than non-volunteers (for recent meta-analytic reviews, see Jenkinson, et al., 2013; Okun, Yeung, & Brown, 2013).

Despite substantial evidence linking helping behavior to better physical health and longevity for the helper, to date, there have been no attempts to formally or systematically explicate the physiological mechanisms that link helping others to the physical health of the helper. Not surprisingly, empirical investigation of such mechanisms is in its infancy (e.g., Cosley, McCoy, Saslow, & Epel, 2010; Poulin & Holman, 2013). We attempt to remedy this state of affairs by proposing a theoretical framework intended to advance knowledge in this area. Specifically, we elaborate a recently developed neurobiological model of prosocial (helping) behavior in an effort to identify neurohormonal circuitry and events responsible for the link between helping and health. We refer to the model, in both its original (S. L. Brown, Brown, & Preston, 2012) and extended forms, as a caregiving system that, like Bowlby's (1969) parental caregiving system, functions to keep offspring safe. But in contrast to Bowlby's system, and others predicated on his account (e.g., Collins & Ford, 2010; George & Solomon, 1999; Mikulincer & Shaver, 2005), ours highlights and details neurophysiological components that regulate caregiving motivation (see also Preston, 2013). Our model also extends the umbrella of the caregiving system well beyond parenting, to encompass a broad array of prosocial and altruistic phenomena.

The bedrock for our model is the *neuroscience* of mammalian parenting, especially Numan's (2006) animal (rodent) model of maternal care. Of course, there are many caveats associated with modeling human behavior in animals (Gottlieb & Likliter, 2004), but in our view, mammalian models can be useful tools for beginning to map the neural

underpinnings of prosocial motivation in humans. The mammalian nervous system is known to be highly conserved across species (Finlay & Darlington, 1995; Krubitzer, 1995), and there are clear caregiving and prosocial behavioral parallels between humans and other mammals, including rodents (Preston, 2013). Moreover, rodent models have already generated data that show considerable promise for advancing our understanding of the origins and neurobiological bases of human prosociality (Carter, 2014), including bonding (Carter, 1998), maternal responsiveness and parental care (Rilling & Young, 2014), empathy (Decety & Svetlova, 2012; Panksepp & Panksepp, 2013), and helping behavior (Ben-Ami Bartal, Decety, & Mason, 2011; Ben-Ami Bartal, Rodgers, Bernardez Sarria, Decety, & Mason, 2014). Rodent models and data are also beginning to yield insights into relationships between sociality, neuropeptides, and health resilience, including factors that are associated with stress-buffering and recovery from wounds (Beery & Kaufer, 2015; Poutahidis, et al., 2013). Importantly, there are also converging human data (Gouin, et al., 2010; Poulin & Holman, 2013).

Our original model, based on Numan's (2006) investigations of maternal care in rodents, describes a set of neural contingencies that may have evolved originally for the purpose of providing offspring care. These neural underpinnings, we argue, offered a regulatory infrastructure that, through genetic and cultural evolution, came to support a more flexible and generalized system of helping behavior, not restricted to biological kin and not readily exploited by cheaters (S. L. Brown & Brown, 2006; S. L. Brown, et al., 2012; Preston, 2013). From a gene-centered evolutionary perspective, the redirection of parental-like care (helping) to non-relatives could have occurred through direct or indirect reciprocity (Alexander, 1987; Nowak, 2006; Trivers, 1971). It may also have

occurred through *fitness interdependence*, a mechanism in which the helper's reproductive success varies directly with that of a recipient (and vice-versa), as in cooperative breeding, cooperative foraging, or defense of coalition members (S. L. Brown & Brown, 2006; Roberts, 2005). Alternatively, directing caregiving responses to those who are not biological relatives may constitute an evolutionary "misfire" (Dawkins, 1989), in which helping mechanisms—shaped when individuals in need were biological relatives or likely reciprocators—are activated in contemporary environments by others in need who are *neither* relatives nor reciprocators.

As for effects on health, we hypothesize that caregiving motivation itself is part of a chain of related biochemical events that function to reduce stress and inflammation and, thereby, promote health. A key stress- and inflammation-reducing agent is the neuropeptide oxytocin (OT) which, according to our model, modulates the neural circuits that coordinate active help and interacts with other hormones that regulate the immune system, especially progesterone. The health implications of our model are premised on the existence of what is now well-documented "crosstalk" between neuroendocrine and immune systems, an interaction that likely has ancient evolutionary roots (Demas, Adamo, & French, 2011). It is not difficult to imagine that enhancements to this neurohormonal-immune interaction might well have paid fitness dividends in our ancestral past, through direct effects on survival and reproduction, and indirect effects on the survival and reproduction of offspring, other biological kin, and even interdependent nonkin.

Because our paper highlights links between stress and the immune system, and between immune system dysregulation and disease, it is important to at least

acknowledge the important relationships between stress, immune system regulation, inflammation, and disease. The growing consensus across the health sciences, including cancer biology, is that often times disease, aging, and even death can be attributed to an underlying dysregulation of the immune system, or prolonged exposure to chronic inflammation. Below, we begin by describing links between stress and immune function. We follow with a summary of our caregiving system model and describe how its features are related to stress regulation and immune function through neural arrangements and hormonal interactions. The final section of our paper presents evidence that is consistent with our analysis of how health may be linked to helping behavior and compares our analysis with alternative approaches to understanding how social behavior influences physical health.

Stress and Immune Function

An important key to understanding the effects of stress on both aging and disease is inflammation, and the regulation of inflammation. Exposure to external or internal threatening stimuli can initiate a fight-or-flight (acute stress) response, one of the effects of which is inflammation—the release of pro-inflammatory cytokines, such as interleukin-6 (IL-6)—that stimulates immune responses. In turn, stress hormones are released. The function of stress hormones (e.g., glucocorticoids such as cortisol) is to inhibit excessive inflammation, which, if left unchecked, can lead to tissue damage. Chronic stress may create resistance to the anti-inflammatory effects of glucocorticoids, resulting in a more aggressive immune response and excessive inflammation (Cohen, et al., 2012; Rohleder, Aringer, & Boentert, 2012). Over time, the resulting dysregulation of the immune system and chronic inflammation can cause or accelerate disease (Clodi,

et al., 2008).

Indeed, repeated activation of the stress response can (a) cause problems with brain function and create neuronal damage (McEwen, 2007), (b) accelerate aging (Kerr, Campbell, Applegate, Brodish, & Landfield, 1991), and (c) contribute to, or accelerate illnesses including asthma, HIV, and inflammatory diseases (e.g., Walser, et al., 2008). Among the ten leading causes of mortality, chronic inflammation contributes to the pathogenesis of at least seven, including cancer, stroke, heart disease, respiratory disease, diabetes, and Alzheimer's Disease (https://www.lef.org/protocols/health_concerns/chronic_inflammation_01.htm).

Within disease subtypes, the immune system is also implicated in the lethality of the disease. For example, the pro-inflammatory cytokine IL-6 creates a lethal feedback loop in the development of cancer whereby detection of a tumor is recognized as a threat to healthy tissue. This threat to the body (as in the case of physical or bacterial assault) recruits IL-6 to stimulate differentiation of stem cells to replace damaged tissue. A feature of IL-6 is that it is able to signal the immune system to ignore inputs from other cytokines and regulatory features that could disrupt or limit differentiation (and proliferation) of stem cells. When this happens, signals from the immune system that would otherwise regulate or limit proliferation of existing cells are ignored, making the tumor grow larger, causing greater release of IL-6 (Korkaya, Liu, & Wicha, 2011). This means that in the case of cancer, attempts to regulate the immune system by interrupting the IL-6 feedback loop should reduce tumor size and the lethality of the cancer. Indeed, tests of this possibility have been supportive (Korkaya, et al., 2012). More broadly, this evidence implies that factors which regulate stress and/or the immune system should help to reduce

not only the development of chronic inflammation and disease, but perhaps also the lethality of disease.

The Extended Neurobehavioral Model of Caregiving

Our model, in its original form (S. L. Brown, et al., 2012), describes neurohormonal circuitry that regulates stress which, if prolonged, may lead to a dysregulated immune system, excessive inflammation, and, over time, health impairment. We hypothesize that repeated activation of caregiving motivation tends to regulate stress and inflammation, attenuating some of their deleterious effects. In extending our model, we argue that this process is mediated in part by the release of oxytocin, based on its documented role in regulating both helping behavior and stress (Carter, 1998, 2014), and its interactions with progesterone. Importantly for health, endogenous and exogenous administration of oxytocin have been shown to regulate stress at a variety of levels, including (a) decreasing blood pressure and the stress hormone cortisol, and (b) increasing progesterone, a regulatory hormone that restores GABAergic tone following activation of the hypothalamic-pituitary-adrenal axis (Childs, Van Dam, & de Wit, 2010). Before elaborating these stress-regulating features of oxytocin and progesterone, we introduce and provide an overview of our extended caregiving model, and discuss its hypothesized neurohormonal circuitry.

Background

Using Numan's (2006) investigations of the neurophysiological bases of maternal care in rodents as a springboard, we advanced a neuroscience model of a human caregiving system (S. L. Brown, et al., 2012). The model has been tested

empirically (e.g., Ho, Konrath, Brown, & Swain, 2014; Konrath, Fuhrel-Forbis, Lou, & Brown, 2012; Poulin, Brown, Dillard, & Smith, 2013; Poulin & Holman, 2013); extended theoretically (Preston, 2013); has served as an organizing framework for a cross-disciplinary effort to better understand prosocial motivation (S. L. Brown, Brown, & Penner, 2012); and has stimulated empirical and theoretical efforts beyond the confines of our own research group (Abelson, et al., 2014; Miller, Kahle, Lopez, & Hastings, 2014) and discipline (Rynes, Bartunek, Dutton, & Margolis, 2012). Below we focus on our extended caregiving model (Figure 1), including its neurophysiological foundation—Numan’s (2006) animal (rodent) model of maternal responsiveness (Figure 2)—and its stress-regulating features. Table 1 serves as a glossary of neuroanatomical and neurophysiological terms found in each figure and/or in the text that follows.

Overview of the Extended Caregiving Model (Figure 1)

Our model, as shown in Figure 1, consists of both behavioral and neural components. Note that this is a model of *other-directed motivation* that can lead to helping others in need, not an all-encompassing theory of helping behavior. Nothing inherent in the model indicates that engagement in helping behavior, by itself, enhances the helper’s health and well-being, or that activation of self-interested motives for helping—for example, compliance with the wishes/demands of others, enhancement of reputation, financial gain, avoidance of punishment—will do so.³ In our model, cues for activating other-directed motivation are primarily the combination of perception of need and relationship variables—for example, the helper’s perception of interdependence with the

individual in need (S. L. Brown & Brown, 2006; Poulin, et al., 2010).

As for caregiving motivation and its consequences, the flow of activity proceeds from the left of Figure 1, beginning with the helper's perception of need, distress, or vulnerability in another person; proceeding to activation of caregiving motivation (center of Figure 1); and ending in health and longevity benefits for the helper (right of Figure 1). Points 1-7 below are intended to serve as an overview of the model, as depicted in Figure 1.

1. The model rests heavily on the evidence-based assumption that cues for need, distress, or vulnerability in offspring trigger caring responses, and that these are accompanied by cortical and subcortical neurohormonal, affective, and cognitive events (Swain, 2011). In the animal model (Figure 2), the amygdala processes cues for the presence of pups and transmits signals to the medial pre-optic area (MPOA) of the hypothalamus. The evidence suggests that some neurons in the amygdala assign negative valences to pups (e.g., in adult virgin female rats), and other amygdala neurons assign positive valences (e.g., in postpartum rats). Other brain regions that may respond to cues for need and send signals to the hypothalamus include the anterior cingulate cortex (ACC), particularly the subgenual area and the orbital frontal cortex (Freedman, Insel, & Smith, 2000; Johansen-Berg, et al., 2008; Haber, Kunishio, Mizobuchi, & Lynd-Balta, 1995; Rempel-Clower & Barbas, 1998).

2. We hypothesize that the helper's genotype, the environment, and the interaction between the two moderate the effects of perceived need in another on motivation to respond prosocially (caregiving motivation). Although fundamental components of parental care and prosocial behavior may have a long evolutionary history, the respective

roles of contributing genetic and environmental factors are likely to be complex, especially considering the remarkable flexibility of animal parental care, let alone human prosocial behavior (Royle, Russell, & Wilson, 2014). Like others (Meaney, 2010), we assume a dynamic and continuous gene-environment interplay, one in which the environment can moderate the effects of genes for prosocial behavior, and genes can moderate the effects of the environment. And we recognize that these effects may not be limited to any single link in the chain of responses regulating caregiving motivation and downstream effects. These assumptions are supported by data. There is considerable evidence for the heritability of prosocial behavior generally (Knafo & Israel, 2010), and recent studies suggest that genetic variations related to oxytocin may have different effects on aspects of caregiving motivation (Peltola, et al., 2014; Poulin & Holman, 2013). There is also evidence-based speculation that the expression of oxytocin-related genes may be modified by early childrearing environments (Kumsta, Hummel, Chen, & Heinrichs, 2013).

3. Resource availability is also hypothesized to moderate the effects of perceived need on caregiving motivation. Resources can be external to the helper (situational), such as the presence of other potential helpers nearby. Resources can also be internal—physiological, cognitive, and emotional (Collins, et al., 2014). Examples of internal resources are vagal tone (Porges, 1998)⁴, prosocial personality traits like compassion (Goetz, Keltner, & Simon-Thomas, 2010), and even aggressive capabilities in certain situations, such as seen in coalitional defense (Díaz-Muñoz, DuVal, Krakauer, & Lacey, 2014), maternal protection of offspring (Wolff, 1985), and competitive altruism (Roberts, 1998).

4. We hypothesize that the helper's perceptions of interdependence and connectedness (having a social bond) with the person in need can also moderate effects of perceived need on caregiving motivation, and these two variables may be especially important for facilitating prosocial behavior that is costly and rendered on a long-term basis (Brown, 1999; S. L. Brown & Brown, 2006). As in S. L. Brown, et al. (2012), we postulate that cells in the medial orbital frontal cortex (MOFC) respond to cues for interdependence and social bonds by communicating with the hypothalamus and activating caregiving motivation. This hypothesis is based on several features of the MOFC. The medial OFC is interconnected with the hypothalamus, the control center of caregiving motivation, and is capable of triggering an oxytocin release (Eisler & Levine, 2002). Moreover, the OFC can integrate messages from different sensory inputs, is sensitive to changes in motivational states, and appears capable of coding for the uniqueness of socially bonded relationship partners. Finally, a link between social bonds and the medial OFC has been demonstrated in studies of human mother-infant bonding (Parsons, Stark, Young, Stein, & Kringelbach, 2013), and is highlighted in a neuro-image-based model of parenting (Swain, 2011).

5. We hypothesize that exposure to an individual in need or distress, and the prospect of rendering assistance, can initiate a short-term stress reaction in the helper, defined in terms of hypothalamic-pituitary-adrenal (HPA) axis activity. The amygdala is assumed to play a role in initiating the stress reaction, firing in response to detection of threatening stimuli. Amygdala activity, along with need, resource, and relationship inputs, is also an important component in priming the MPOA, the hypothesized motivational control center for orchestrating prosocial behavior (Numan, 2006).

6. Need and relationship inputs are hypothesized to stimulate the release of neurohormones (e.g., oxytocin) into the MPOA, producing other-directed prosocial states and emotions (e.g., compassion). Such states are important for suppressing competing self-interested motives, such as the motivation to avoid or escape personal danger (S. L. Brown & Brown, 2006; Sober & Wilson, 1998), and for facilitating approach behavior and appropriate helping responses (Numan & Insel, 2003). Indeed, the animal model of parenting behavior highlights the role of the oxytocin-primed MPOA in interrupting avoidance motivation by interfering with inputs from the amygdala to the pariaqueductal grey, a neural circuit for mobilizing resources for sympathetic arousal (the “fight-or-flight” response). As we discuss in greater detail later, there is now considerable evidence that oxytocin, under certain circumstances, plays a role in downregulating stress (Carter, 2014; Kanat, Heinrichs, & Domes, 2014).

7. Hypothesized downstream consequences of oxytocin release include the release of progesterone, a sex steroid that tends to downregulate prolonged stress. A growing body of evidence suggests that progesterone facilitates homeostasis of various systems (Bitzer, 2009), including the immune system (Jain, Kannan, Prouty, & Jain, 2004; Tamura et al., 2011). We hypothesize that it is the stress- and immune-regulating features of oxytocin and progesterone that are responsible, at least in part, for health and longevity benefits observed in individuals who help others in need.

Below we consider the features of the model in greater detail, with special emphasis on neural circuitry, the inhibition of fear and stress, responding to need in others, and neuroendocrine modulation of caregiving system activation.

Neural Circuitry

The most prominent neural component in the model is the medial preoptic area of the hypothalamus (MPOA), which is hypothesized to regulate caregiving motivation, in conjunction with other brain regions (e.g., the amygdala) and hormonal or neural substrates (e.g., progesterone, oxytocin). The MPOA has been identified in animal models as the motivational basis for maternal care, arguably an evolutionary progenitor of more complex forms of prosocial behavior (Preston, 2013). The MPOA organizes downstream active parenting responses (e.g., nest building, pup-retrieval) through its interactions with important reward structures in the brain, especially the ventral tegmental area (VTA), nucleus accumbens (NAcc), and ventral pallidum (VP), an organizational center for motoric helping responses (Numan, 2006). Specifically, the MPOA signals the ventral tegmental area to release dopamine into the NAcc. Dopamine then binds to D1, *inhibitory*, receptors in the nucleus accumbens (Numan, et al., 2005). Because the NAcc normally inhibits the VP (Numan, 2006), the MPOA's inhibitory effect on the NAcc results in facilitation of motoric helping responses (Figure 2). Thus, through the process of releasing the accumbens' inhibitory hold on the ventral pallidum, the MPOA is able to generate parental behavior.

Part of the evidence for the motivational role of the MPOA in parental behavior comes from the fact that normal maternal behavior cannot occur when there is significant damage to the MPOA, VTA, or the VP (Numan & Insel, 2003). For example, MPOA damage interferes with maternal responses that are voluntary and active (e.g., pup retrieval), but does not interfere with other maternal responses such as nursing (reviewed in Numan, 2006). Moreover, other behaviors and bodily functions that are also under the

control of the hypothalamus such as motor behavior, sexual behavior, hoarding, activity levels, body weight, and temperature regulation are not altered with damage to the MPOA.

Inhibiting Fear and Stress

Data from studies of rodents suggest that the MPOA influences helping behavior not only by facilitating approach via inhibitory inputs to the accumbens, but also by inhibiting fear and stress. In natural conditions, hormones associated with pregnancy, birth, and lactation (e.g., a high estrogen:progesterone ratio, oxytocin, prolactin) inhibit the default fear reaction to rat pups. It is also the case that these hormones function to down-regulate stress reactions to other stimuli during the postpartum period, including reduced synthesis and release of stress hormones, and accompanying reductions in anxiety and fear (Chauke, de Jong, Garland, & Saltzman, 2012).

The possibility that prosocial behavior involves the inhibitory regulation of stress is not new, and is highlighted prominently in neuroimaging studies of human empathy that reveal partial inhibition of the physical pain network in response to observing another in need (e.g., Decety & Meyer, 2008). At a neurological level, the motivational basis for parenting works in opposition to the stress response, which compels an animal to avoid, abandon, or even attack a pup. The avoidance/stress neural circuit includes initial projections from the amygdala that trigger the anterior hypothalamic nucleus (AHN) to mobilize resources for sympathetic arousal via activation of the periaqueductal grey (PAG). The amygdala—AHN—PAG link (i.e., avoidance motivation/sympathetic stress) is interrupted in cases in which the MPOA directs maternal behavior, presumably because it inhibits the AHN and/or the PAG (Numan, 2006; Rosenblatt & Mayer, 1995).

Indeed, the MPOA has been shown to have inhibitory interconnections with the PAG (Lonstein & Stern, 1997).

This portion of the neural arrangement deserves emphasis because when considered with the approach pathway, the implication is that stress must have been regulated if helping behavior is observed. In other words, activation of the motivational command center for helping behavior, the MPOA, sends a signal to interrupt transmission between the amygdala and the sympathetic stress response (i.e., PAG) which would have led to an avoidance response (as opposed to a helping response). If parenting or helping behavior is observed, then stress regulation must have occurred at some level, assuming engagement of this particular neural circuitry. Moreover, this neural arrangement implies that if MPOA activation is stronger than avoidance motivation, then parenting behavior will occur in response to need. Indeed, virgin animals who have no exposure to pregnancy hormones, and who would otherwise kill or cannibalize a pup, will actually initiate parenting behavior (taking care of pups) if there is damage to any part of the avoidance/stress circuit—the amygdala, AHN, or PAG (Bridges, Mann, & Coppeta, 1999; Fleming, Vaccarino, & Luebke 1980; Sheehan, Paul, Amaral, Numan, & Numan 2001; Sukikara, Mota-Ortiz, Baldo, Felicio, & Canteras, 2006). Another way to characterize this evidence is that the mere absence of avoidance motivation is sufficient to disinhibit parental behavior in response to pups.

The fact that prolonged exposure to pups can stimulate “parenting” behavior in virgin animals suggests not only that stress normally inhibits caregiving motivation, but also that it does not depend solely on parental status or pregnancy for activation. In effect, the

neural architecture of the parental care system ensures that it can be activated in individuals who are not parents (or pregnant).

Responding to Need in Others

Based on Numan's work with rodents, stress appears to have paradoxical effects on maternal behavior. Although stress may inhibit parenting behaviors, it also appears capable of *priming* caregiving motivation at an earlier stage, when adult animals are first exposed to pups. According to Numan's model, on exposure to pups, the adult's medial amygdala (MeA) activates her MPOA by transmitting olfactory (and non-olfactory) cues that function as a barometer for assessing danger or need. We hypothesize that a similar "needs assessment" occurs in humans, driven by homologous neural circuitry and events. In effect, our threat sensors are activated by another's need—their stress, if you will. The amygdala transmits these threat signals to the MPOA, moderated by an assessment of interdependence with the individual in need, and perceived availability of resources (Figure 1).

Whether caregiving motivation is activated depends on downstream resolution of approach-avoidance conflicts. Because the amygdala has been implicated in the processing of highly salient negative (or positive) emotional states (e.g., Adolphs, Russell, & Tranel, 1999; Ohman, 2005), and appears to be centrally involved in orchestrating the stress response (LeDoux, 2000), it is an ideal candidate for registering need in others. However, there are also other neural regions that appear capable of alerting individuals to threat or need in others, including the subgenual anterior cingulate cortex (sgACC) and the medial orbital frontal cortex (MOFC). These two regions are connected with one another (Kringelbach & Rolls, 2004), and with subcortical regions

involved in maternal care, including the hypothalamus, PAG, and nucleus accumbens (Freedman, et al., 2000; Johansen-Berg, et al., 2008; Haber, et al., 1995; Rempel-Clower & Barbas, 1998).

Interestingly, neuroimaging studies of humans reveal that both the sgACC and the MOFC become active when adults observe infants. For example, the sgACC becomes active when mothers listen to infant cries (Lorberbaum, et al. 1999; Lorberbaum, et al., 2002), and the MOFC becomes active during the visual presentation of infant as compared to adult faces (Kringelbach et al., 2008). Moreover, the sgACC has been directly linked to human altruism (Moll, et al., 2006), and some investigators have hypothesized that the OFC provides direct access to caregiving motivation, through the disinhibition of the paraventricular nucleus of the hypothalamus (Eisler & Levine, 2002). Consistent with the possibility that attending to need in others regulates stress, the sgACC is involved in parasympathetic control, modulates stress hormones, and mediates emotional responses in humans, particularly sadness (see Preston, 2013, for a review), which has been linked experimentally to the motivation for helping behavior (Cialdini, et al., 1997). Together, this work suggests an intimate connection between perceiving need in others, responding to threat, and stress regulation.

Although perceived threat may be important for activating the caregiving system, the resulting sympathetic arousal must somehow be modulated by the MPOA to enable caregiving behavior, or at least this would be the implication of the animal model described above. Following Numan's (2006) logic and extending his animal model, our model suggests that neuropeptides and hormones modulate activation of the caregiving system by increasing signal strength in the MPOA, which would decrease the chance that

amygdala activation will mobilize sympathetic stress, and increase the likelihood of engaging in prosocial behavior. Below we describe these neuroendocrine influences.

Neuroendocrine (Oxytocin) Modulation of Caregiving System Activation

To understand possible neuroendocrine influences on the caregiving system, it is necessary to consider the role and action of pregnancy hormones. The MPOA has numerous receptors for pregnancy hormones and for the neuropeptide oxytocin (OT). Oxytocin is important to investigate because of its known general association with closeness, attachment, affiliation, parenting and other forms of prosocial behavior. Thus, unlike estrogen, which is also a pregnancy hormone, but has been studied primarily in relation to reproductive processes among females, oxytocin—along with vasopressin, prolactin, and endogenous opioids—is considered to be part of the neurochemical basis for love, social affiliation, and parenting behavior across gender, type of relationship, and species (Carter, 1998). This makes oxytocin an appealing candidate for modulating activation of the caregiving system, especially in the context of close or interdependent relationships between the helper and recipient. Below we describe evidence linking oxytocin to prosocial behavior and the regulation of stress, including stimulating the release of the stress-regulating hormone progesterone. Because progesterone plays a critical role in regulating stress and the immune system, and also in coordinating physiological homeostasis, its release may be key to understanding mechanisms that link prosocial behavior to better health in humans.

Oxytocin and prosocial behavior. In nonhuman mammals, oxytocin triggers the onset of parental behavior (S. L. Brown & Brown, 2006). In humans, oxytocin has been linked to a variety of interpersonal behaviors associated with prosocial motivation, including

trust (Baumgartner, Heinrichs, Vonlanthen, Fischbacher, & Fehr, 2008), charitable donations and generosity (Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005; Zak, Stanton, & Ahmadi, 2007), in-group favoritism (De Dreu, Greer, Van Kleef, Shalvi, & Handgraaf, 2010), and parental responses to infant cues (Feldman, et al., 2010; Naber, van IJzendoorn, Deschamps, van Engeland, & Bakermans-Kranenburg, 2010; Riem et al., 2011). Oxytocin is also implicated in other social and affective phenomena that are presumably related to effective caregiving. For example, oxytocin enables social memory (Ferguson, et al., 2000), including the recognition of faces (Rimmele, Hediger, Heinrichs, & Klaver, 2009; Guastella Mitchell, & Dadds, 2008; Savaskan, Ehrhardt, Schulz, Walter, & Schachinger, 2007). Oxytocin also can facilitate the interpretation of social cues (Domes, Heinrichs, Michel, Berger, & Herpertz, 2007), empathy (Bartz et al., 2010), and possibly the recognition of fear (and therefore need) in others (Fischer-Shofty, Shamay-Tsoory, Harari, & Levkovitz, 2010). Perhaps the most convincing evidence for a link between oxytocin and prosocial behavior in humans comes from studies of individuals who are notably deficient in their ability to recognize need and help others, as is the case in individuals suffering from autism spectrum disorder (e.g., Asperger's syndrome). In these individuals, nasal administration of oxytocin has stimulated prosocial behavior (Andari, et al., 2010), and facilitated the recognition of emotion in others (Guastella et al., 2010).

Although research generally supports a causal role for oxytocin in prosocial actions and behavior (Insel, 2010; Lukas et al., 2011; Van IJzendoorn & Bakermans-Kranenburg, 2012), a sizable body of the human oxytocin work shows effects that are context-specific (Bartz, Zaki, Bolger, & Ochsner, 2011), qualified by whether there is interdependence

with the recipient (e.g., Kosfeld, et al., 2005; De Drue, et al., 2010), a history of maternal love or adverse developmental experiences (Riem, et al., 2013), and polymorphisms of the gene coding for the oxytocin receptor (Kumsta, et al., 2013). Together, these and the other studies we have reviewed up to this point suggest that oxytocin's prosocial effects are facilitated by well-specified relational and developmental conditions, in some cases, the very conditions that appear to be moderators of caregiving motivation (e.g., interdependence and social bonding). Based on these studies as well as evidence discussed below, it is reasonable to hypothesize that the release of oxytocin, in response to variables such as interdependence, primes the caregiving system, increasing the chance of its activation.

Evidence that oxytocin may prime the caregiving system comes in part from the fact that there are OT receptors throughout the maternal care circuit, including the MPOA (Brunton & Russel, 2008), that are associated with pair bonding and the active care of offspring (Insel & Young 2001). Oxytocin (and other pregnancy hormones) are not necessary for parenting behavior, as virgin animals, juveniles, and males will also engage in parenting behavior in response to the presentation of pups (Numan, 2006). However, latency of onset of parental behavior is slower in non-mothers, unless they are administered oxytocin, suggesting that oxytocin (and other hormones associated with pregnancy) increase the speed and readiness of parenting behaviors, but are not necessary for their occurrence (Numan, 2006). In rats, oxytocin is associated with the onset of maternal behavior, and the hormonal events associated with pregnancy increase oxytocin receptors in the MPOA and other regions (Numan & Insel, 2003). However, once maternal behavior is established, it cannot be blocked with oxytocin antagonists. In

summary, the work on oxytocin suggests that it may be important in priming the caregiving system, but may not be the direct cause of parental behavior, or more generalized forms of prosocial behavior.

Oxytocin and Stress Regulation. Oxytocin has a paradoxical relationship with stress. On the one hand, oxytocin has been shown to down-regulate stress responding, specifically by reducing HPA axis activity (Carter, 1998), decreasing blood-pressure and cortisol (Uvnäs-Moberg, 1997; Uvnäs-Moberg, 1998a, b), and decreasing functional coupling between the amygdala and the PAG (Kirsch et al., 2005), which would interfere with mobilizing sympathetic stress in response to threat.

On the other hand, oxytocin is also known to be a stress hormone. For example, in humans, exogenous OT leads to improved recall of adverse events (Bartz et al., 2010) and heightened startle responses to stimuli that are psychologically distressing (Grillon et al., 2013; Striepen, et al., 2012). A recent study in mice indicates that oxytocin potentiates fear responses by binding to receptors in the lateral septum (Guzman et al., 2013). Studies of the neural substrates of pain show that oxytocin actually mediates the effect of substance P, an activator of the sympathoadrenal system, on cardiovascular responses (Maier, et al., 1998). Interestingly, OT was shown early on to modulate, or to release, ACTH in restraint and other forms of stress (Gibbs, 1986; Link, Dayanithi, Fohr, & Gratzl, 1992), causing some researchers to speculate that anti-inflammatory effects of oxytocin are due to stimulating effects of OT on corticosterone levels (Iseri et al., 2005). However, the association of OT with ACTH was not explored in depth (Viero, et al., 2010), and some evidence demonstrates the opposite effect, showing that OT attenuates the ACTH response (Parker, Buckmaster, C., Schatzberg, A., & Lyons, D., 2005).

Evidence that OT may mediate and trigger stress hormones under some circumstances contributes to a view of oxytocin as a stress hormone, which excites sympathetic neurons in the spinal cord (Coote, 1995). Indeed, thoracic and lumbar level injections of OT in rats cause increased heart rate and blood pressure respectively (Richard, Moos, & Freund-Mercier, 1991).

We do know that OT is released from two different sources in the hypothalamus—the paraventricular nucleus and the supraoptic nucleus (Neumann, Toschi, & Veenema, 2006), and that OT has both glutamatergic (excitatory) and GABAergic (inhibitory) effects (Qi, et al., 2012; Young-Hwan, Stoeckel, M., Freund-Mercier, & Schlichter, 1998), and that there are two different types of OT neurons (magnocellular and parvocellular, Yang, Wang, Han, & Wang, 2013), perhaps keys to understanding the paradoxical effects of OT on stress. We do not know the circumstances that determine whether OT's effects on stress will be excitatory or inhibitory. Possibilities include the particular pathways involved in the binding of OT to its receptors, and downstream effects on hormones that regulate stress, such as progesterone. Progesterone is especially important to consider in light of its role in physiological homeostasis, including the regulation of the immune system which has important implications for physical health.

Oxytocin and Progesterone.

Progesterone is a steroid that increases in the second part of the menstrual cycle to prepare for pregnancy, and it increases tenfold during pregnancy, coordinating many of the functions needed to provide nutrients to the fetus and protect it from disease and injury. Typically, during pregnancy, it is the withdrawal of progesterone that increases oxytocin and stimulates the onset of labor and maternal behavior (Rosenblatt, Siegel, &

Mayer, 1979). And, a progesterone antagonist, RU-486, has been shown to increase oxytocin, which suggests that progesterone can have an inhibitory effect on the oxytonergic system (Thomas, Crowley, & Amico, 1995). Consistent with this possibility, progesterone has been shown to be related to social behavior in ways that seem opposite from oxytocin, for example, progesterone can impair social recognition in animals (Bychowski & Auger, 2012).

Despite evidence of inhibitory effects of progesterone on oxytocin, and evidence that oxytocin has inhibitory effects on progesterone release, much of this work also reports that oxytocin *at very low doses* can have a stimulating effect on progesterone release (Barrett & Wathes, 1990; Berndtson, Weaver, & Fortune, 1996; Chandrasekher & Fortune, 1990; Miyamoto & Schams, 1991; Tan, Tweedale, & Biggs, 1982a, b), including modulating effects of hGC (Human Granulosa-Lutein cells) on progesterone release (Mayerhofer, Sterzik, Link, Wiemann, & Gratzl, 1993). Moreover, the pattern of effects of progesterone in response to social stimuli in humans resembles that observed for oxytocin. For example, a study of social closeness among women demonstrated that progesterone increased in response to closeness, and that it predicted increased prosocial motivation one week later, measured as the willingness to sacrifice one's life for a partner (S. L. Brown, et al., 2009b). Among males and females, a film clip depicting attachment and bonding caused progesterone to increase among viewers (Wirth & Schultheiss, 2006).

Summary

We have highlighted the role of stress in cellular inflammation, immune system function, illness, and aging. We have also described our extended caregiving system

model, proposing that oxytocin-priming of the medial pre-optic area of the hypothalamus is the neurohormonal concomitant of activation of caregiving (helping) motivation. We argued further that the caregiving-related release of oxytocin, in interaction with progesterone, promotes stress and immune system regulation, thereby enhancing the helper's health and longevity. We cautioned that these hormonal influences appear complex and, in some instances, even paradoxical. In the next section we consider this complexity in greater detail, and conclude that it may be pivotal in understanding links between helping others, health, and longevity.

Hormonal Influences on Stress, Immune Function, and Disease

The evidence to date (reviewed below) raises the possibility that (a) low-dose oxytocin—an hypothesized driver of caregiving motivation—has an *indirect* effect on stress regulation, mediated by progesterone; and (b) that it is the repeated release of progesterone that tends to regulate health-threatening effects of *prolonged* stress, contributing to the well-being and longevity of the helper.

Oxytocin. OT has been shown to modulate immune responses (Yang, Wang, Han, & Wang, 2013). For example, in vitro OT (along with vasopressin) has been shown to diminish IL-6 release from the neurointermediate pituitary lobe (Spangelo, deHoll, Kalabay, Bond, & Arnaud, 1994). OT injected subcutaneously has been shown to reduce the (TNF)-alpha response to oxidative injury of the colon in Sprague-Dawley rats (Iseri, et al., 2005). OT has also been shown to release prostacyclin, which is a molecule that inhibits platelet aggregation, helping to prevent blood clots (Williams & Tahir, 1980). A recent study of healthy men indicates that oxytocin alleviated the cytokine and chemokine response to bacterial endotoxin, including reduction of tumor necrosis factor

(TNF)-alpha, Il-1 receptor antagonist, Il-4, Il-6, macrophage inflammatory protein-1alpha, macrophage inflammatory protein 1-Beta, monocyte chemoattractant protein-1, interferon inducible protein 10, and vascular endothelial growth factor, or VEGF (Clodi, et al., 2008). Because OT treatment did not show direct effects on cytokine expression in vitro, the study's authors hypothesized that effects of OT on cytokine release may be explained by indirect effects of OT on the activity of the vagus nerve, which contains an anti-inflammatory pathway. Consistent with this possibility, OT has been shown to prime the excitability of vagus neurons (McCann & Rogers, 1990).

The paradoxical effects of oxytocin on stress extend to the immune system, perhaps not surprisingly. These influences of oxytocin on immune function include cell proliferation, causing inhibition under some circumstances but also augmenting cell proliferation as the hormonal milieu changes (Whittington, et al., 2007). Oxytocin has also been shown to stimulate Cox-2, an enzyme that has been linked to an increased risk for cancer (Bakhle, 2001), in the uterine tissue of pregnant cows (Fuchs, Rust, & Fields, 1999). Evidence that oxytocin may be related to the etiology of mental health problems and disease comes from studies that show a correlation between circulating levels of oxytocin and symptoms of post-traumatic stress disorder and disassociation in humans (Seng, et al., 2013; Munro, et al., 2013). And, postmortem brain levels of oxytocin show that OT is substantially elevated in the hippocampus of individuals with Alzheimer's Disease (Mazurek, Flint, Beal, & Martin, 1987).

Together this work suggests that the influence of oxytocin on stress and health is not clear cut. That is, the relationship of oxytocin to stress, inflammation, and disease appears to be context-dependent. This paradoxical relationship of oxytocin to stress and immune

function means that the mechanisms linking prosocial behavior (or any form of social behavior) may not be reducible to only the actions of oxytocin. Our analysis therefore suggests that oxytocin alone cannot account for the health benefits of prosocial behavior. Instead, we focus on potential down-stream effects of oxytocin on progesterone, which is known to have important influences on homeostasis in general, and the immune system in particular.

Progesterone. Traditionally, progesterone has been studied as a female reproductive hormone, a sex steroid that is produced in the ovaries and adrenal glands, known for its role in establishing and maintaining pregnancy (Douglas, 2010). Recent research, however, notes that progesterone is also produced in the brain and spinal cord in both men and women (Stein, Wright, & Kellermann, 2008). Importantly, the action of progesterone, and metabolites such as allopregnanolone (ALLO), upregulates the inhibitory neurotransmitter GABA in the brain, which helps to promote protective and restorative processes. Following a stressor, progesterone and its metabolites restore normal GABAergic tone and axis activity (Childs, et al., 2010). The fact that progesterone and its metabolites upregulate GABA is interesting in light of studies that show that a GABA agonist can block the release of ACTH caused by substance P (Coiro, et al., 1992). Recall that as described above, oxytocin has been shown to mediate the effect of substance P on increased ACTH. This could mean that in the presence of progesterone, it is theoretically possible that oxytocin would not release ACTH, and, therefore, that progesterone may have the power to limit possible exacerbating effects of oxytocin on stress hormones and inflammation. Indeed, Coiro, et al. (1992) speculate that

in humans GABAergic mechanisms regulate the action of substance P—which presumably includes the effect of substance P on oxytocin release.

The possibility that oxytocin sometimes triggers progesterone release could account for the demonstration that oxytocin is related to a long-term decrease of blood pressure in rats, despite the fact that the half-life of oxytocin is too short to lead to a decrease in blood pressure (Petersson, Alster, Lunderberg, & Uvnäs-Moberg, 1996). Although the mechanism accounting for decreased blood pressure was not determined, the pattern of findings is consistent with the possibility that oxytocin led to a progesterone release. Specifically, the decrease in blood pressure exhibited a progesterone signature as it was more pronounced for females than for males, and varied with the day of the menstrual cycle. Moreover, independent studies have established that progesterone can lower blood pressure directly (Regensteiner, et al., 1991; Rylance, et al., 1985; see Barbagallo, et al., 2001, for a review).

In addition to its stress-regulating role, progesterone may limit exposure to inflammation in ways that do not leave an individual vulnerable to infection and disease. There is evidence consistent with this possibility. For example, progesterone has been shown to activate tumor necrosis factor (TNF) – alpha (Jain, et al., 2004) while blocking TNF-alpha induced COX-2 (Tamura, et al., 2011), an enzyme described above that has been linked to cancer. On the other hand, progesterone does not block TNF-alpha induced manganese superoxide dismutase (Mn-SOD), a gene that protects cells against oxidative stress caused by cytokines (Hawk, Viner, Dannenberg, & DuBois, 2002). This suggests that progesterone may activate what appears on the surface to be a harmful cell-signaling protein—TNF-alpha—but that by selectively blocking COX-2 and not Mn-

SOD, progesterone in essence is helping the body build antioxidants while limiting exposure to inflammation.

Thus, progesterone, unlike oxytocin, may have a “stress conditioning” effect (Weinert & Timiras, 2003, pg. 171), in which its role in regulating (and activating) the immune system builds superoxide dismutase, which would help the body repair tissue damage caused by exposure to stress and inflammation over the life-span. Such a role for progesterone would be critical in terms of health because it is the accumulating insults to homeostatic balance caused by oxidative stress and inflammation that have been proposed as one of the primary theories of senescence, aging, and death; whereas the activation of superoxide dismutase has been hypothesized, and shown, to increase lifespan (Weinert & Timiras, 2003).

Together, this work suggests that progesterone’s ability to enhance beneficial effects of the immune system could prolong survival. Consistent with this possibility, a review of the neuroprotective effects of progesterone conducted by 20 research groups with 4 species concluded that protective effects are likely due to progesterone’s ability to limit or reduce free radical damage (Stein, et al., 2008). A more recent review concluded that neuroprotective effects of progesterone are accomplished through multiple pathways, such as reducing edema, enhancing the survival of neurons, and modulating inflammation and cellular apoptosis (Deutsch, et al., 2013). Suggestive evidence that these immune system effects translate to human survival comes, in part, from several cancer studies showing that women in the luteal phase of their menstrual cycle, when progesterone levels rise, have better surgical outcomes. Attempts to evaluate this possibility experimentally using a randomized control trial of women with operable breast cancer showed that a

single dose of progesterone given before surgery significantly improved disease-free survival and overall survival rates in node-positive patients (Badwe, et al., 2011).

Progesterone is critical for a variety of systems, beyond regulating the stress response and inflammation. Specifically, progesterone promotes homeostasis and regulation of a variety of other bodily functions, including using fat for energy; normalizing blood sugar, zinc, and copper levels; and restoring cell oxygen levels (see Bitzer, 2009, for a review). In the central nervous system, both animal studies and human data suggest that progesterone can improve outcomes for a variety of neurological diseases, ranging from traumatic brain injury and spinal cord injury to motoneuron disease and seizures (Deutsch, et al., 2013). The neuroprotective functions of progesterone are thought to act at a variety of levels including normalizing the blood-brain barrier, increasing GABA, and decreasing oxidative stress, cellular apoptosis, and the release of inflammatory cytokines (Stein, et al., 2008).⁵

Direct Tests of Mechanisms that Link Caregiving Motivation to Physical Health

Our model, consistent with considerable evidence, suggests that (a) stress accompanies the perception of, and reaction to, others in need; and (b) the MPOA, primed by hormones such as oxytocin and progesterone, down-regulates the sympathetic stress response in the context of interdependence, close social bonds, and prosocial behavior. Put simply, we hypothesize that stress-relieving and restorative properties of this neural arrangement and these neuropeptides mediate the relationship between helping others and the helper's health. Although tests of the model are in their initial stages, accumulating evidence suggests that stress-buffering is an important step in the chain of events linking prosocial behavior to improved health.

For example, the provision of emotional support to a partner has been shown to accelerate recovery from a laboratory stressor (Floyd et al., 2007), reduce perceived stress (Floyd, et al., 2005; Floyd, 2006), and reduce the stress hormone cortisol, which can be harmful to health with prolonged exposure (Sapolsky, Uno, Rebert, & Finch, 1990; Sapolsky 1996). Moreover, in investigations of the health benefits of religious behavior, a stress-buffering effect of active help was found such that financial difficulties, presumed to exacerbate stress, were less likely to be associated with mortality among individuals who had helped others (Krause, 2006).

Direct tests of our caregiving system model have shown that performance on a reaction-time task accelerates recovery from a stress induction, but only under conditions in which participants believe their performance will benefit a partner (S. L. Brown, et al., 2015). Among older bereaved spouses, the provision of support to others predicts accelerated recovery from depression, but only among those with a heightened stress response (S. L. Brown, et al., 2008). A prospective study of mortality demonstrated that exposure to stressful life events was unrelated to mortality risk for older adults who had helped someone in the past year, while stressful life events were strongly related to mortality risk for those who had not helped others; specifically, mortality risk doubled with exposure to each subsequent stressful event (Poulin, et al., 2013). Poulin and Holman (2013) report convergent findings from an independent prospective study. They found that charitable behavior (e.g., donating blood, giving money to or working for a charitable group) assessed at baseline appeared to buffer the relationship between stressful events and new-onset (physician-diagnosed) physical ailments reported over the course of two years. Importantly, their findings also suggest a moderating role for

genotypic factors, specifically, the single nucleotide polymorphism (snp) oxytocin receptor, OXTR-rs53576. Stress buffering was evident for individuals carrying the A allele (AA/AG), but not for homozygous carriers of the G allele (GG). Taken together, these data suggest that prosocial behavior may mitigate harmful effects of exposure to stressors by ameliorating or buffering the effects of physiological and psychological stress.

Studies examining the direct effect of caregiving system activation on progesterone, oxytocin, and immune function are underway, and demonstrate that oxytocin predicts increased progesterone and lower systolic blood pressure when individuals help someone they feel close to, but that oxytocin predicts increased blood pressure, or increased cortisol and decreased progesterone in control conditions involving helping a stranger or helping oneself (S. L. Brown et al., 2015). Other findings from this study show decreases in cytokines and growth factors (i.e., IL-6, IL-8, and TGF-Beta) among participants who helped a close partner, but not for those who helped a stranger or themselves.

Alternative Explanations and Limitations

Alternative Causal Mechanisms

Despite a clear link between helping others, on the one hand, and health and longevity benefits for the helper, on the other, insufficient data exist to support definitive statements regarding underlying cause-effect mechanisms. We have hypothesized that activation of caregiving motivation sets in motion a train of neurohormonal events that down-regulates stress and inflammation, and has restorative effects on the body. But because the bulk of supportive behavioral evidence from human studies is correlational, there are alternative explanations for the link between helping and health. It is possible,

for example, that healthier individuals are more likely than the unhealthy to be helpers; that is, helping is an effect, not a cause, of good health (e.g., Bertrand, et al., 2011; Thoits & Hewitt, 2001). According to this view, selection bias that favors healthy helpers—not helping itself—is responsible for observed health advantages of helpers over non-helpers. Although this alternative explanation may be attractive because of its parsimony, evidence to date suggests that, by itself, it is not sufficient to explain positive health and longevity benefits for helpers who are volunteers (Jenkinson, et al, 2013), or informal caregivers (R. M. Brown & Brown, 2014). Recent meta-analyses show a significant drop in mortality for volunteers, even in the face of adjustments for sociodemographic, economic, lifestyle, and physical and mental health status (Jenkinson, et al., 2013; Okun, et al., 2013). And in the case of informal caregiving, mortality reductions are maintained in prospective studies even when health covariates are controlled at baseline (e.g, S. L. Brown, et al., 2003, 2009a), or when helpers and non-helpers are carefully matched on health propensity scores⁶ (Roth, et al., 2013). But the crucial test of the healthy caregiver hypothesis is to assess the health status of individuals *before* they become caregivers, and track them over time. Of the few studies that have met this criterion, only one (to our knowledge) has reported a health advantage for pre-caregivers (McCann, Hebert, Bienias, Morris, & Evans, 2004⁷). The remaining studies show that individuals who eventually transition into caregiving had *poorer* health from the outset—before adopting the role of caregiver—compared to non-caregivers (Burton, Zdaniuk, Schulz, Jackson, & Hirsch, 2003; Chepngeno-Langat & Evandrou, 2013; Lee & Gramotnev, 2007; Tooth & Mishra, 2014⁸).

Another possible explanation of the health benefits of helping is that caring for others may indeed have a positive causal impact on health, but not because of the activation of caregiving neural circuitry. Rather, according to this account, the health advantage of helpers is due to the fact that they engage in healthier behaviors than non-helpers—for example, helpers get more physical exercise and/or maintain better health habits (e.g., Fredman, et al., 2008). These views are not mutually exclusive; in theory, healthier individuals may be more likely to help others, and may also derive benefits from their helping behaviors. However, while helpers may be more physically active than non-helpers, and activity may help offset health decline in some groups of caregivers (Fredman, et al., 2008), there is little direct evidence to indicate that greater amounts of physical activity or better health behaviors are, by themselves, responsible for the health and longevity advantages of helpers overall (R. M. Brown & Brown, 2014; Jenkinson, et al., 2013; Konrath, et al., 2012; Okun, et al., 2013).

Determinations of how well these alternative explanations perform relative to our caregiving model await more systematic research. Especially important are additional longitudinal investigations that track individuals before, during, and after helping experiences, comparing those who transition into and out of helping roles with those who remain non-helpers throughout the course of the study. Also needed are experimental studies that randomly assign individuals to helping and non-helping conditions, control for physical activity, and monitor resulting changes in stress indicators, such as selected hormones and cardiovascular reactivity (e.g., S. L. Brown, et al., 2015).

Ethical and Technological Limitations

Other limitations of our account of the benefits of helping include ethical considerations that prevent *experimental* investigations of the underlying neural circuitry of the caregiving system in humans, and existing brain imaging tools that are insensitive to the temporal sequence implied by our analysis. We cannot determine, therefore, whether the medial orbital frontal cortex selectively signals oxytocin to prime the MPOA's inhibition of the stress response, and release disease-fighting interactions between oxytocin and progesterone. Nevertheless, this possibility suggests patterns of relationships among brain regions, neuropeptides, hormones, and immune markers that can be examined empirically. For instance, if our caregiving system model is correct, helping a loved one should create a positive association between oxytocin and progesterone, which may be discernible in blood samples or receptor densities using PET imaging. Similarly, helping a loved one may create a different pattern of connectivity in the brain relative to helping oneself. These patterns can then be associated with markers of inflammation and with stress reactivity or recovery. If results of such studies show sufficient promise, there may be reason to conduct clinical trials with progesterone and/or a combination of oxytocin and progesterone in an effort to examine the specific disease-fighting predictions of our caregiving system model, such as whether the joint effect of low dose oxytocin and progesterone increases or builds TNF-alpha released MnSOD. Aside from their bearing on our caregiving system model, these types of studies would constitute a new area of investigation that links behavior, motivation, and stress, with neural circuitry, cardiovascular, endocrine, and immune markers in an effort to understand mechanisms that mediate between social behavior and disease and mortality.

In this way, a model for understanding the complexity of a variety of biomarkers could be practical and useful, independent of the pattern of results it generates.

Limitations of Animal Models

Finally, our model is predicated upon the existence of similarities between rodent and human parenting neurophysiology and behavior. However, generalizing from rodent maternal care observed in the lab to human caregiving (and other prosocial behaviors) in natural settings can be risky. Not only are there differences in observational settings (laboratory vs. nonlaboratory) to consider, but also the ways in which parental caregiving and other forms of prosocial behavior are operationally defined—for example, pup retrieval in rats (Preston, 2013) vs. informal caregiving (R. M. Brown & Brown, 2014) and volunteering (Okun, et al., 2013) in humans. In addition, there are species differences in gene expression and brain organization that must be considered. As Gottlieb & Lickliter (2004) note, the same genes can be expressed differently in different species, and there appear to be important differences in brain organization across mammals, even between humans and other primates (let alone between humans and rodents).

Indeed, there are likely to be important species differences—within and between phylogenetic classes—in the ways that a “caregiving system” is instantiated in the brain, and the ways in which the system’s activation is predictive (or independent) of physical health. For example, although oxytocin and other neuropeptides are present in both mammals and birds, the density and location of their receptors (and, presumably, function) can vary greatly, even within closely related species (van Anders, Goodson, & Kingsbury, 2013). Moreover, in some highly social species (e.g., various species of ants and bees), the caregiving brain circuitry we have described does not exist (Gronenberg,

2008; Menzel & Giurfa, 2001), and yet there are robust demonstrations of altruism in both ants (Hollis & Nowbahari, 2013) and bees (Rueppell, Hayworth, & Ross, 2010), and even evidence for help-related cellular repair in foraging honeybees (e.g., Baker, Wolschin, & Amdam, 2012).

That said, there are compelling reasons for suspecting that rodent-human similarities in neural systems that support parental care are more than superficial (Lucion & Bortolini, 2014; Rilling & Young, 2014). Such similarities may well reflect conservation of neural structure and function across mammals generally (Nelson & Panksepp, 1998) and, based on neural analysis with deep brain stimulations (DBS), conservation of the “CARE/maternal nurturance system” in particular (Panksepp & Panksepp, 2013). Accordingly, mammalian animal models of caregiving, like our own, seem well-positioned to function as “sources for ideas, hypotheses, and research directions” (Gottlieb & Lickliter, 2004) for investigations of human prosocial motivation and its health consequences. Ideally, such investigations will provide a testing ground not only for model-generated predictions, but also for the adequacy of the model’s assumptions.

Conclusions

We and others have suggested that human prosocial behavior is rooted in the evolution of maternal caregiving, and facilitated by neurochemical events that accompany caregiving, especially the release of progesterone and oxytocin (S. L. Brown, et al., 2009a; S. L. Brown, et al., 2012; Preston, 2013). Based on these models, we have hypothesized that it is the stress-buffering properties of these hormones that account for now well-documented beneficial correlates of prosocial behavior. There is considerable evidence to implicate both oxytocin and progesterone in the regulation of stress and

inflammation. Moreover, oxytocin appears to have paradoxical effects: (a) it can both inhibit and exacerbate stress; and (b) it can both inhibit and stimulate the release of progesterone. Taken together, the evidence to date warrants confidence that oxytocin plays a role in activating caregiving motivation, that there is a complex relationship between oxytocin and progesterone, that both oxytocin and progesterone can affect the regulation of stress, and that progesterone can enhance immune system regulation. Precisely how the release of progesterone is accomplished, however, is less clear. Based on the paradoxical effects of oxytocin on progesterone release, we have speculated that it is initiated by low-dose oxytocin associated with caregiving activation. Further research addressing these issues is important, not only for assessing the role of caregiving motivation in enhancing health and longevity, but also for identifying potential mechanisms—behavioral, neurohormonal, cellular, and molecular—by which hormones like oxytocin and progesterone regulate stress and promote immune system regulation. Like others (e.g., Wirth, 2011), we believe such research must cross disciplinary boundaries and may well form the basis for clinical applications in the future.

Our extended model, and its theoretic progenitor, selective investment theory (Brown & Brown, 2006), make precise predictions about how and under which circumstances prosocial behavior may be beneficial for physical health. Specifically, perceptions of interdependence between helper and individual in need, and activation of social bonds based on interdependence, should be the most effective triggers for releasing stress-reducing, restorative, and protective neuromodulators. For example, our analysis suggests that high levels of interdependence will bias threat and pain activations to trigger oxytocinergic release of progesterone, as opposed to oxytocinergic activation of

sympathetic stress. If this set of relationships is empirically supported, a next step would be to follow the causal chain and examine the implications for the cytokine response, as a function of whether OT does or does not release progesterone. For example, it would be interesting to replicate fear conditioning paradigms and measure both oxytocin and progesterone to determine whether the presence of a loved one or interdependent partner causes oxytocin and progesterone to become positively correlated.

Following the causal chain, a next step would be to determine whether the effects of progesterone on stress and immunity differ as a function of the source of progesterone, whether it is released by oxytocin or luteinizing hormone. Similar analyses could be conducted for oxytocin, to determine whether the mechanisms of action of oxytocin on the vagus nerve, for instance, are different depending on whether it is released in the presence or absence of progesterone. Finally, we need to disentangle beneficial effects of progesterone from its downstream metabolite, ALLO, which also has neuroprotective effects and regulates cholesterol homeostasis (Irwin, Wang, Chen, & Brinton, 2012).

When integrated with human studies that employ neuroscientific techniques such as functional neuroimaging and hormone assays, neurobehavioral approaches to caregiving system motivation, such as ours, can generate testable hypotheses that may improve understanding of fundamental relationships between social behavior, stress, well-being, and health. Future studies, for example, should attempt to determine whether health problems previously attributed to social isolation (House, Landis, & Umberson, 1988) and loneliness (Hawkley & Cacioppo, 2010) are due, in part, to lack of engagement of the caregiving system. In our view, this is a worthy venture not only because it may help resolve longstanding issues related to the health benefits of social contact—for example,

whether it is better to give or to receive social support (Thomas, 2010)—but also because it may help clarify the roles of neuropeptides in regulating stress. Studies that examine relationships between oxytocin, progesterone, and ACTH might help disentangle stress-reducing and stress-augmenting properties of oxytocin found in the literature.

Also needed are systematic investigations of sex differences in caregiving system activation and its consequences. Considerable evidence indicates that men are more likely to provide active, assertive, and heroic help to strangers under conditions that involve threat or danger, while women are more likely to provide nurturance and sensitive emotional support to friends and family members (Eagly, 2009). It is also the case that sex differences favoring females exist in vulnerability to and recovery from a variety of physical stressors and diseases, including responses to bacterial pathogens (García-Gómez, et al., 2013), development of autism spectrum disorders (ASD, Werling & Geschwind, 2013), and outcomes following brain injury (Roof & Hall, 2000). Moreover, there is evidence to suggest that female parity predicts reductions in all-cause mortality (Simons, Simons, Friedlander, & McCallum, 2012). Neurohormones associated with caregiving activation may help explain these observed sex differences. For example, based on animal studies, Carter (2007) speculates that vasopressin, in particular, may have sexually dimorphic effects, including increased male vulnerability to ASD; alternatively, oxytocin or its receptors may explain female resistance to ASD. And a large number of animal investigations of progesterone have shown its remarkable capability for promoting and enhancing tissue repair following brain injury (Deutsch, et al., 2013; Stein, 2008).⁹ In terms of our model, it remains for future studies to illuminate possible moderating effects of biological sex on the neurohormonal circuitry of caregiving

motivation, and on subsequent modulation of stress, inflammation, immunity, and cell repair.

Beyond benefits for basic science, there are potentially important payoffs for understanding and treating stress-related diseases. Mounting evidence links psychosocial stress to the proinflammatory cytokine IL-6 (Rohleder, et al., 2012), which in turn is linked to a variety of potentially debilitating health problems, including cardiovascular disease (e.g., Yudkin, Kumari, Humphries, & Mohamed-Ali, 2000), depression (Dowlati, et al., 2010), Alzheimer's Disease (Swardfager, et al., 2010), and colorectal cancer (Guthrie, Roxburgh, Horgan, & McMillan, 2013). If the activation of caregiving motivation releases hormones that inhibit IL-6 and other pro-inflammatory responses, then it will be important to reconsider views of caregiving (including relevant social policies) that emphasize the negative, burdensome nature of helping the sick, disabled, and elderly. It will also be important to identify those factors that activate versus thwart the caregiving system, and find ways to promote interdependence, social bonds, and prosocial behavior. Doing so may turn out to be no less important (or urgent) than developing new drugs or other medical treatments designed to reduce the incidence of, or recovery from, stress-related disease.

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Footnotes

¹ The term, “prosocial behavior”, is used by psychologists to refer to “a broad category of acts that are defined by some significant segment of society and/or one’s social group as generally beneficial to other people” (Penner, Dovidio, Piliavin, & Schroeder, 2005, p. 366). Accordingly, *prosocial behavior* encompasses a broad category of helping phenomena, including what evolutionary scientists (e.g., evolutionary biologists, evolutionary psychologists, behavioral ecologists, and behavioral economists) refer to as “altruism”—behavior that enhances the fitness of the recipient of the help, but diminishes the fitness of the helper (West, Griffin, & Gardner, 2007).

² A case in point is the oft-cited finding that informal caregiving elevates caregiver mortality, reported in three published investigations. In one of these studies, caregiver status was assumed but not established (Christakis & Allison, 2006). In another, there was evidence of increased caregiver mortality in some age-gender groups, but not in others, and mortality rates overall were lower in caregivers than in non-caregivers (Fredman, et al., 2008). In the third study, Schulz and Beach (1999) found that their samples of caregivers were 63% more likely than noncaregivers to die within four years. However, their caregiver samples consisted of spouses who were *disabled*, while the noncaregiver controls were not, thus confounding disability with caregiving, and rendering mortality differences between caregivers and controls uninterpretable. All other investigations of caregiver mortality published to date—larger-scale and better controlled—have not only failed to replicate this effect, but have reported just the opposite: informal caregiving is associated with *reduced* mortality (S. L. Brown, et al.,

2009a; Fredman, Cauley, Hochberg, Ensrud, & Doros, 2010; O'Reilly, Connolly, Rosato, & Patterson, 2008; Roth, et al., 2013).

³ Whether health and well-being benefits accrue to helping motivation that is self- as opposed to other-directed is an open empirical question, but studies to date are suggestive. Crocker, Canevello, Breines, & Flynn (2010) found that other-directed (compassionate) motivation in university students was associated with a reduction over time in anxiety and dysphoria, while self-directed motivation produced the opposite effect. And, using data from over 10,000 participants in the Wisconsin Longitudinal Study, Konrath, et al. (2011) documented an inverse relationship between volunteering and mortality, but only for participants who volunteered for other-directed (altruistic) reasons. The mortality risk of those who volunteered for self-directed reasons was no different from that of non-volunteers.

⁴ The term “vagal tone” refers to the extent to which vagus nerve impulses inhibit heart rate, a measure of parasympathetic activity in mammals. The term is sometimes used interchangeably with respiratory sinus arrhythmia (RSA), the rhythmic pattern of heart rate associated with normal respiration. According to Porges (1998), changes in RSA may reflect the status of the social engagement system. Indeed, vagus nerve activity may have made mammals uniquely suited to parental caregiving and other forms of prosocial behavior. In the context of the present discussion, it is easy to imagine that extremely low or extremely high levels of vagal inhibition might impede adaptive responding to individuals in need of help. (Kogan, et al., 2014).

⁵ Reports of beneficial effects of progesterone stand in contrast to findings from landmark studies which linked synthetic progesterone to the breast cancer-causing effects of

hormone replacement therapy (e.g., Beral, 2003). Note however that adverse effects of hormone replacement therapy in postmenopausal women have since been attributed to combinations of estrogen and synthetic progesterone (Chlebowski, et al., 2013), or to complex and context-dependent interactions involving the progesterone receptor (Hagan, & Lange, 2014). There have been very few investigations of the effects of *endogenous* progesterone on cancer in premenopausal women, partly owing to the difficulty in obtaining reliable and interpretable measures during the menstrual cycle. However, the evidence to date does not implicate naturally-occurring progesterone in the development of breast cancer in premenopausal women, and some studies show a significant inverse correlation between progesterone and incidence of breast cancer (Muti, 2014).

⁶ “Propensity Score Matching” refers to the conditional probability that an individual in the entire sample—in this case, *both* caregivers and noncaregivers—is a caregiver, *given* the set of covariates specified (e.g., health, age, education, marital status, etc.).

Caregivers and noncaregivers are matched *only* on their propensity scores, not on each individual covariate.

⁷ There are potential problems with the design of the McCann, et al. study, the most serious of which is that non-caregiver control status may have been confounded with care recipient status (R. M. Brown & Brown, 2014).

⁸ Tooth & Mishra (2014) found that the effect of pre-caregiver health was different in each of their cohorts. For their 1973-78 cohort, individuals who transitioned into caregiving had poorer health and health behaviors than those who remained non-caregivers. For their 1946-1951 cohort, pre-caregiver health status had no effect.

⁹ Although results from the first placebo-controlled clinical evaluations of progesterone's effects on traumatic brain injury in humans yielded promising results consistent with animal findings (Wei & Xiao, 2013), more recent large-scale experimental studies have failed to replicate the advantage of progesterone (Skolnick, et al., 2014; Wright, et al., 2014).

Table 1

Neuroanatomical and Neurophysiological Terms Used in the Text and Figures of this Article

Abbreviation	Term
ACTH	Adrenocorticotrophic hormone
ALLO	Allopregnanolone
AHN	Anterior Hypothalamic Nucleus
DA	Mesolimbic Dopamine System
DLPFC	Dorsolateral Prefrontal Cortex
GABA	Gamma-Aminobutyric Acid
HPA	Hypothalamic-Pituitary-Adrenal
IL-6	Interleukin-6
Mn-SOD	Manganese Superoxide Dismutase
MeA	Medial Amygdala
MPOA	Medial Preoptic Area of the Hypothalamus
MOFC	Medial Orbital Frontal Cortex
NAcc	Nucleus Accumbens
OFC	Orbital Frontal Cortex
OT	Oxytocin
PAG	Periaqueductal Gray
TNF	Tumor Necrosis Factor
sgACC	Subgenual Region of the Anterior Cingulate Cortex
VEGF	Vascular Endothelial Growth Factor
VP	Ventral Pallidum
VTA	Ventral Tegmental Area

Figure Captions

Figure 1. The proposed “Extended Neurobehavioral Model of Caregiving Motivation”.

NOTES: Connecting arrows are excitatory, and lines terminated by a bar are inhibitory. The figure is a revised and extended version of the original model (Brown, et al., 2012). Neural structures and mechanisms are premised on Numan’s (2006) animal model of maternal care (see Figure 2 caption and text). See Table 1 and Figure 2 caption notes for definitions of terms.

Figure 2. The animal model of maternal care (after Numan, 2006).

NOTES: The hormonally-primed medial preoptic area of the hypothalamus (MPOA) has two main effects: Suppression of avoidance and activation of the mesolimbic dopamine (DA) system.

Pup stimuli activate mother’s medial amygdala (MeA) and the MPOA.

Hormonal priming of the MPOA inhibits avoidance, and activates the ventral tegmental area (VTA). VTA output binds with D1 inhibitory receptors in the nucleus accumbens

(NAcc), depressing its output. The result is disinhibition of the ventral pallidum (VP), facilitating instrumental maternal responsiveness.