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REVIEW ARTICLE

Positive Social Interactions in a Lifespan Perspective with a Focus on Opioidergic and Oxytocinergic Systems: Implications for Neuroprotection

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Abstract: In recent years, a growing interest has emerged in the beneficial effects of positive social interactions on health. The present work aims to review animal and human studies linking social interactions and health throughout the lifespan, with a focus on current knowledge of the possible mediating role of opioids and oxytocin. During the prenatal period, a positive social environment contributes to regulating maternal stress response and protecting the fetus from exposure to maternal active glucocorticoids. Throughout development, positive social contact with the caregiver acts as a "hidden regulator" and promotes infant neuroaffective development. Postnatal social neuroprotection interventions involving caregiver–infant physical contact seem to be crucial for rescuing preterm infants at risk for neurodevelopmental disorders. Attachment figures and friendships in adulthood continue to have a protective role for health and brain functioning, counteracting brain aging. In humans, implementation of meditative practices that promote compassionate motivation and prosocial behavior appears beneficial for health in adolescents and adults. Human and animal studies suggest the oxytocinergic and opioidergic systems are important mediators of the effects of social interactions. However, most of the studies focus on a specific phase of life (*i.e.*, adulthood). Future studies should focus on the role of opioids and oxytocin in positive social interactions adopting a lifespan perspective.

Valentina Colonnello

Keywords: Social interactions, social bond, compassion, development, neuropeptides, opioid, oxytocin.

HIGHLIGHTS

- Animal and human studies linking social interactions and health are reviewed
- A positive social environment has a protective role for health and brain functioning
- Oxytocin and opioids mediate the effects of social interactions
- Psychobiological studies of social interaction should adopt a lifespan perspective

INTRODUCTION

The warmth of comforting social contact and the joy of friendly interactions fuel our daily positive social exchanges. Recent years have witnessed an increased interest in the psychobiological foundation of positive social interactions, especially their associated emotional feelings and their protective role for an individual's health throughout life. Positive social interactions may have protective effects for health, both directly, through their regulatory role in an individual's physiological functions [1, 2], and indirectly, through their buffering of responses to stressful life experiences [3, 4]. Among the neurobiological systems underlying the positive effects of social interactions and stress response regulation, the opioidergic and oxytocinergic systems are considered to play a central role due to their widespread receptor distribution in several central and peripheral autonomic nervous systems and in endocrine tissues [5-11].

Endogenous opioids are able to regulate the synthesis and release of stress-induced hypothalamic-pituitary-adrenal (HPA) axis corticotropin-releasing factor [12, 13] and modulate the activation of sympathetic and cardiovascular systems [14-16]. As rat [17-19], monkey [20, 21], and human studies [22-25] indicate, endogenous opioids are essential for social bonding and mediate sensitivity to social reward. In addition, the opioidergic system is implicated in soothing physical pain and emotional distress, and its activation has an adaptive and protective role for the organism [7, 26, 27].

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The opioidergic system works in concert with the oxytocinergic system, which is implicated in stress regulation and processing the salience of social stimuli [9]. In animals, administration of oxytocin increases social motivation [28] and induces soothing feelings similar to those induced by actual social stimuli, as measured by the reduction of distress vocalizations in isolated infants [29]. In humans, oxytocin administration dampens cortisol levels following psychological stress [30], facilitates autonomic cardiac control [31], and modulates amygdala activation to threatening stimuli [32]. Of note, central release of oxytocin regulates output of the vagal dorsal motor nucleus, thereby regulating bodily functions associated with the parasympathetic nervous system [33]. The vagus nerve innervates a wide range of organ systems in the body and as such is well positioned to provide feedback about the state of the organism to the brain [34]. For this reason, vagal functioning (mainly indexed by heart rate variability, HRV) acts as an integrative biomarker for both biological (*e.g.*, immune dysfunction and inflammation) and psychological (*e.g.*, emotion regulation) measures. The adaptive effects of social behavior for emotional and physical health may be explained by the intrinsic and mutual physiological connection between oxytocin and vagal functioning [33].

In this context, the present contribution reviews studies on the role of positive social interactions for individual health and their implications for neuroprotection, with a special focus on current knowledge of the possible mediating role of opioids and oxytocin. Of note, current neuroprotection interventions not only encompass pharmaceutical treatments but also include social strategies that promote typical neurodevelopment, prevent or mitigate neurodisabilities, and enhance brain functionality after neuronal injury.

Recently, compassion-focused meditation has been at the center of scientific investigation due to its potential neuroplastic properties. The ability to experience compassion, instead of empathetic distress, when facing others' or our own suffering has been shown to provide long-term benefits to health and well-being. Thus, evidence of how compassion-focused meditation-based interventions affect neuroprotection will also be considered.

Given the importance of animal research for understanding emotions associated with social affiliation and given the burgeoning literature showing that positive social interactions have impact throughout development, we will adopt a translational and lifespan perspective (Table **1**). We will review studies indicating that a positive social environment contributes to the protection of the fetus from exposure to maternal stress responses, the role of the caregiver for infant neuroaffective development, and the importance of attachment figures and friendships in adulthood for health and brain functioning, with positive effects on brain aging. In each section of this paper, the role of opioids and oxytocin in positive social interactions will be reviewed.

The examined social interactions are those that play a key role throughout life: interactions with the mother (caregiver), peers, and partner. The interaction with one's own caregiver has both functional and structural effects. At a functional level, a soothing effect, induced by the mother's opioidergic, oxytocinergic, and parasympathetic nervous systems activation, has been consistently shown. At a structural level, the activity of such systems indirectly influences brain plasticity and neural development. The other examined forms of social interaction are those with peers and significant others. As people age, the social support gained from interactions with peers and significant others has been associated with protective effects on physical and psychological health. Indeed, social support enhances resilience to stress, presumably *via* its effects on the HPA system, the parasympathetic branch of the nervous system, and central oxytocin pathways. At a structural level, this appears to counteract brain aging and reduce the likelihood of neurodegenerative diseases, consistent with the concept of neuroprotection, which is by definition the mechanism resulting in the recovery or regeneration of the cells, structure, and function of the nervous system.

From Prenatal Stress to Protective Effects of Social Support

There is now a wealth of evidence indicating a continuity between prenatal and postnatal social experiences and that social environment, interacting with genetic factors, contributes in shaping individual development from early in life. While still in the womb, the fetus is already sensitive to environmental stimuli [35, 36] as well as to changes in maternal hormonal and emotional states [37-39]. Among the mechanisms mediating the effects of maternal social experience on fetal development, the maternal HPA stress axis activation level and the associated release of active glucocorticoids are considered to play a key role [38, 40].

Under moderate levels of maternal stress, the fetus is relatively protected from exposure to maternal glucocorticoid release thanks to the action of the placental enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) that converts active glucocorticoids into inactive glucocorticoids [41, 42]. However, excessive levels of maternal glucocorticoids may not be fully metabolized by the placenta and, thus, may reach the fetus [43].

Maternal social and emotional experiences may indirectly influence fetal neuromaturation and an infant's later health. For example, gestational stress has a strong impact on the fetal brain and postnatal behavioral phenotype. Guinea pigs exposed to prenatal environmental stress have elevated basal plasma cortisol levels, decreased plasma testosterone, and increased anxiety-like responses, though these effects are dependent on offspring sex and timing of the prenatal stress [44]. Prenatally stressed rats show social impairment [45-47], adrenal hypertrophy [48], reduced brain derived neurotrophic factor (BDNF) expression in the prefrontal cortex and striatum [49], and altered brain organization and function, such as reductions in cerebral asymmetry, dopamine turnover, and amygdala gene expression and reactivity [46, 47].

In humans, exposure to psychosocial maternal stress during the prenatal period is associated with risk of socio-emotional disorders [50, 51], HPA axis dysregulation [52], and telomere length shortening in offspring [53]. Telomeres, which are protective protein-DNA structures that cap chromosomes, shorten with cell division and oxidative

Table 1. Overview of main correlates of neuroprotective factors for each developmental stage in animals (A) and humans (H).

Developmental Phase	Modulating Factors	Biochemical Changes	Psychosocial Correlates
Gestation	• Positive social interactions for future mothers (H) • Social support from partners (H)	• Reduced maternal HPA stress axis activation (H) • Increased plasma oxytocin in mothers (H) • Reduced systolic blood pressure (H) • Normal child's body length and weight (H)	• Positive outcomes with respect to postpartum emotional distress and infant reactivity to novelty (H) • Promotion of mother-infant attachment formation (H)
Early infancy	• Skin-to-skin contact (H) • Massage (H) • Touch, warm temperature, and pleasant auditory stimuli (A) • Licking and grooming (in rats) (A)	• Increased vagal tone during the neonatal period (H) • Decreased plasma beta-endorphin and cortisol (H) • Increased endogenous oxytocin levels (A,H) • Enhanced levels of GRs (A) • Increased gastric motility and body weight (H) • Protective effects for early brain development (A,H)	• Increased mother–infant synchrony at 3 months in preterm infants (H) • High physiologic self-regulation, exploration, and cognition in preterm infants (H) • Reduced anxiety-like responses (A)
Youth	• Positive social experiences (A,H) • Compassionate feelings and interactions (H)	• Increased expression of BDNF (A) • Cortical gene expression of IGF1 (A) • Increased dendritic arborization in the medial prefrontal cortex (A) • Increased heart rate variability (H) • Increased neural survival and synaptogenesis (H)	• Increased emotion processing and learning (A,H) • Increased social learning and emotion regulation (A,H)
Adulthood	• Companionship of partner (A) • Social support during exposure to stress (H) • Self-generated feelings of compassion, social connection, and positive affects toward others (H)	• Enhanced oxytocin levels in the paraventricular nucleus of the hypothalamus (A) • Regulation of cardiovascular reactivity and circulating levels of corticosterone (H) • Reduced cortisol reactivity (H) • Increased telomere length (H) • Reduction of C-reactive protein (H) • Reduced interleukin-6 levels after a stress task (H) • Dampening of HPA activation in response to stress (A,H)	• Decreased anxiety-like behaviors (A) • Protection against cognitive impairment (H)
Elderhood	• Social support (H) • Compassion-focused meditation (H) • Social interaction after stroke (A)	• Increased leukocyte telomere length (H) • Reduced proinflammatory NF-κB-related gene expression in circulating leukocytes (H) • Increased hypothalamic oxytocin gene expression (A) • Lack of age-related atrophy of brain grey matter (H) • Attenuated infarct size, neuroinflammation, and oxidative stress following experimental stroke (A)	• Reduced risk of mortality (H) • Attenuated dysfunctional responses to stress (H)

stress; a shorter telomere is considered a marker of cell senescence [54-56]. Furthermore, maternal psychosocial stress increases risk of prematurity [57, 58], slows rate of development [59], and increases likelihood of psychological disorders [44]. High stress levels during pregnancy have also been associated with increased risk of mental and motor impairments in eight-month-old infants [60]. In a large prospective study, Davis and colleagues [61] found an association between maternal psychological stress due to loss of close relatives during the six months before conception or during the first trimester of gestation and offspring's later risk of schizophrenia. Thus, regulation of maternal stress and associated glucocorticoid levels may be one pathway to protecting fetal neuronal development.

In both animals and humans, an environment that facilitates regulation of the maternal HPA axis through positive social interactions acts as a neuroprotective factor for fetal development. For example, social enrichment protocols, such as communal nesting, which implies social interaction availability during gestation and lactation, promote infant social development in rats [62]. In humans, studies on natural variation in positive social interaction availability during pregnancy indicate that perceived social support from a partner is associated with reduced cortisol levels in response to psychological distress [63], better outcomes with respect to postpartum emotional distress and infant reactivity to novelty [64], normal child body length and weight [65], and facilitated development of mother–infant attachment [66]. Furthermore, programs to promote coparenting quality have positive effects on birth weight, gestational age, and hospitalization length in women with high prenatal cortisol levels [67].

Although the effects of social support on opioidergic and oxytocinergic activity during pregnancy and their effects on fetal development remain scarcely investigated, existing studies suggest that opioid and oxytocin systems may be involved in the positive effects of partner' support. Specifically, opioids and oxytocin mediate social interactions in animals [68-70] and humans [71-72]. Of note, physical and social warmth share similar psychobiological mechanisms, and both are mediated in part by the opioidergic system [26]. In humans, presenting pictures of one's romantic partner reduces sensitivity to experimentally induced pain [73], whereas administering naltrexone, an opioid antagonist, reduces feelings of social connection [74].

Positive social interactions are also associated with high oxytocin levels. For example, women who report greater social support from their partners have higher plasma oxytocin before and after close contact with their partners, in conjunction with lower systolic blood pressure after close positive contact [75]. That study involved non-pregnant women, but endogenous opioids have differential inhibitory effects on stress-induced oxytocin release throughout gestation [76-78].

Taken together, these studies highlight the stress-regulating role of positive social interactions during the gestation period. Future studies should explore the role of the synergic activity of opioidergic and oxytocinergic systems in the protective function of partner support throughout the gestation period.

The Power of the Caregiver's Touch

In the past decade, an effort has been made to identify physiological variables implicated in children's social development. The HRV has emerged as an early physiological marker of regulatory functioning in both preterm and full-term infants [79, 80]. Specifically, infant HRV appears to be a predictor of mother–child interactions, with lower infant vagal tone associated with more disruptive interaction patterns in full-term infants [80]. This is particularly important for social development in preterm infants. For instance, Feldman [81] found that vagal tone during the neonatal period predicted mother–infant synchrony at 3 months in preterm infants. In a subsequent study, preterm infants with lower cardiac vagal tone received less maternal positive affect and gaze in the postpartum period and reduced maternal touch at 3 months compared to preterm infants with higher vagal tone [82]. Poehlmann *et al*. [83] found that, from age 4 to 24 months, preterm infants' postfeeding vagal regulation was positively associated with the mothers' positive affect and involvement and the infants' positive affect and social competence. Vagal tone regulation also has protective effects in terms of later developmental outcomes in preterm infants. For example, in very low birth weight infants, fewer behavior problems at 5 years [79] and higher social competence at school age [84] were both predicted by HRV.

During face-to-face interactions and physical contact, mothers engage in a process of regulating infant physiology [85]. During this process, both mothers and infants reciprocally adapt their heart rhythms, ultimately forming biological synchrony in the acceleration and deceleration of heart rates. Importantly, such bio-behavioral synchrony in the first months of life predicts the development of self-regulatory and interactive capacities across the first years of life in both preterm and full-term infants [79, 81].

Due to infants' high brain plasticity, possible adverse effects of birth difficulties may be significantly reduced by several postnatal social neuroprotection interventions involving caregiver–infant physical contact. For example, skin-to-skin (or kangaroo mother care) programs that encourage close physical contact between caregiver and infant improve health conditions in preterm and low birth weight infants [86, 87]. The soothing effects of touch on infant reactivity to stress have been widely reported. Mother–infant contact induces a comforting effect, as measured by infant heart rate, crying, and grimacing during a standard painful heel lance procedure [88, 89]. In addition, systematic sessions of infant massage facilitate bond formation [90, 91], increase ECG-measured vagal activity, gastric motility, and body weight [92]. Moreover, massage therapy constitutes a beneficial early intervention for infants of mothers with postpartum depression (reviewed in [93]) or autistic children (reviewed in [94]). In a series of studies, Feldman and colleagues have also demonstrated that caregiver–infant skin-to-skin contact facilitates physiologic self-regulation, exploration, and cognition in preterm infants [86, 95, 96]. Furthermore, skin-to-skin contact intervention is associated with decreased plasma beta-endorphin and cortisol in preterm human infants [97].

The positive effects of caregiver–infant physical contact found in human studies agree with animal data, indicating that the caregiver acts as a "hidden regulator" for an infant's autonomic, feeding, and stress-regulation systems [98]. Adult rats that received high maternal care, through licking and grooming, show reduced anxiety-like responses, enhanced levels of glucocorticoid receptors (GRs), and differences in spine density and hippocampus synaptic plasticity [99, 100]. Furthermore, female offspring of high-caring mothers showed increased oxytocin receptor expression [101]. The positive effects of caregiver–infant social contact rely on the orchestration of several evolutionarily preserved neuro-

modulators involved in initiating and maintaining physical proximity between caregiver and infant. For example, the opioidergic system induces a soothing and analgesic effect by reducing infant emotional distress reactivity, increasing comforting feelings, and enhancing pain thresholds [7, 27].

Mother-infant physical contact is also positively associated with rat pups' hypothalamic oxytocin concentration levels [102], and the endogenous production of oxytocin is important for early brain development. Oxytocin receptors are spread throughout several areas of the infant brain [10], and prenatal social experiences contribute to shaping oxytocinergic brain organization. For example, in rats, offspring of prenatally stressed mothers show alterations in brain and behavior development consisting of increased aggressiveness and anxiety-like behavior along with a decreased number of oxytocin-positive magnocellular neurons [103]. In addition, prenatal stress is associated with deficits in social behavior together with reduced oxytocin messenger RNA (mRNA) in the paraventricular nucleus and increased oxytocin receptor binding in the central amygdala [104]. However, postnatal administration of oxytocin into the central amygdala counteracts behavioral deficits due to prenatal stress [104], increases nociceptive thresholds, and reduces corticosterone levels [105, 106]. Oxytocin administration also increases neural growth factor (NGF) levels in the hypothalamus [107], promotes gene expression of BDNF in the right hippocampus in rats [108], and mediates brain organization [109]. In natural conditions, the effects of several social-related nonnoxious stimuli, such as touch, warm temperature, and pleasant auditory stimuli, are likely mediated by changes of endogenous oxytocin levels [75, 110, 111]. A similar effect can be obtained artificially; repeated massage-like stroking in rats, which mimics social grooming, has been shown to induce oxytocin release [112].

In sum, positive interactions in this period of life are associated with healthy neurodevelopment, and they help counteract the adverse effects of birth difficulties. Thus, neuroprotection programs promoting oxytocinergic and opioidergic system activation through caregiver–infant positive contact may be crucial for rescuing preterm infants at risk for neurodevelopmental disorders while constituting the foundation for psychobiological reserves for later adverse life experiences.

The Formation of the Caregiver-Infant Bond

Several mammalian species develop selective and persistent attachment bonds within social affiliative interactions. Through positive caregiver–infant interactions, infants are likely to form a secure attachment bond characterized by feelings of safety and confidence, pleasure from positive social encounters/reunions, and balance between affiliative and exploratory urges [113]. The formation of inner secure attachment models in humans enhances the ability to prompt feelings and representations of safety and emotional security in times of distress [113, 114]. A positive caregiver–infant bond is, thus, a central protective factor for infant socio-emotional and cognitive development. The availability of positive social interactions with the caregiver is thought to facilitate the development of cortico-limbic and subcortico-limbic brain structures essential for emotion regulation [115]. Infants reared within a safe and stimulating social environment are likely to develop emotion regulation skills [116] and cognitive abilities [117]. Moreover, supportive parenting moderates the adverse effects of biological vulnerability for the development of psychopathological symptoms during adolescence [118].

By contrast, disruption of caregiver–infant social bonds has been recognized as a risk factor for impaired neuro-affective and behavioral development [119-123]. For example, in rhesus monkeys, maternal deprivation induces a reduction of social behaviors, an increase of agonistic behavior, an inability to use social companionship as a stress- response buffer, and a reduction in cerebrospinal fluid oxytocin [70]. Rats separated from their mother have decreased BDNF receptors [124], increased cell death of neurons and glia [125], and impaired social behavior [126]. In degus, the disruption of mother–infant bonds induces changes in brain organization of serotoninergic and dopaminergic innervation, similar to the changes found in early socially traumatized humans [127], and alteration of social motivation toward novel social partners [128]. In human infants, challenging social rearing conditions are associated with impaired ability to use social buffering in times of stress and alteration of oxytocinergic system functioning. For example, children reared within a positive family have enhanced oxytocin plasma levels when they interact with their mothers following a moderately stressful experience; such oxytocinergic response is not evident in children who experienced early neglect [129].

Within an attachment bond, individual recognition, feelings of confidence, and caregiver–infant tuning are fundamental. These abilities seem to be mediated by the oxytocinergic and opioidergic systems. Specifically, individual recognition and processing of social information is facilitated by oxytocin administration [9]; in oxytocin knockout mice, social recognition ability is impaired [130, 131], and it is restored following infusion of oxytocin in the amygdala [131]. Moreover, oxytocin administration decreases distress responses associated with social isolation while it increases feeling of confidence in humans [132] and animals [29], and it enhances emotion recognition [133], which is fundamental for emotional attuning.

The amount of intimate interaction and comforting caregiver-infant contact is partly mediated by the opioidergic system. The stress-dampening effects of caregiver–infant interactions are modulated by endogenous opioid release [134]. Studies of mu-opioid receptor gene (OPRM1) polymorphism in rhesus monkeys indicate that OPRM1 C77G polymorphism is associated with high levels of separation distress and reduced social interaction with other group members [20]. In humans, children carrying the OPRM1-G allele have high withdrawn scores and enhanced electrophysiological sensitivity to others' emotional expressions [135]. Thus, the opioidergic system is likely involved in subjective emotional experiences of social proximity and safety, and natural variations in this system are associated with different degrees of sensitivity and resilience to social stress. Altogether, these studies indicate that positive caregiver–infant bonds act as a protective factor for neural

development and influence brain plasticity as a function of individual genetic background.

Affiliative Bonds with Group Members

During development, social affiliative bonds progressively extend to group members other than the caregiver, and the time spent with agemates in playful interactions increases. In children, the salience of peer interactions increases and formation of the first close friendship is central to daily life.

Although the study of positive peer relationships and their effects on neurodevelopment has received little attention, the extant literature indicates that peer interactions play a key role in neuroaffective and emotion-regulation development [136, 137]. Examples of the beneficial effects of positive social interactions on development derive from both experimental agemate deprivation studies in animals and from observational studies on children's peer interactions.

The typical friendly social exchanges detectable in young animals are playful interactions. The positive affects associated with play activity are evident in place preference tests: rats show place preference for places where they previously experienced playful interactions [138]. Not only is play activity pleasant, it also contributes to shaping brain and behavioral development. For example, play experiences increase the expression of BDNF in regions relevant for emotion processing and learning, such as the amygdala and the dorsolateral frontal cortex [139]. In addition, peer play activity is associated with cortical gene expression of insulin-like growth factor 1 (IGF1), which promotes neural survival and synaptogenesis [140] and stimulates stroke-induced neurogenesis [141, 142]. Social interactions with peers during the play period facilitate dendritic arborization in the medial prefrontal cortex [143, 144], an area important for social learning and emotion regulation. In female rats, positive social interactions enhance gene expression of Fos and tyrosine hydroxylase proteins in specific cell groups of the dopaminergic system [145], which is likely underactivated in several human disorders, such as depression [146, 147] and Parkinson's disorder [148, 149]. Of note, animal studies of the neurochemical foundations of joyful social interactions led to the identification of the medical agent, GLYX-13, a partial agonist for glycine receptors, which is considered a promising antidepressant for treatment-resistant depression in humans [150, 151].

Friendly peer interactions affect individual socio-emotional development. For example, animals deprived of peer interactions during the peak play period show social impairment during social encounters [152] and increased anxiety responses when facing novel environments [153]. Furthermore, socially isolated rats show alterations in the reward processing system, such as increased sucrose consumption [154], self-administration of cocaine [155], and enhanced amphetamine- and alcohol-consumption contextual learning, as shown in conditioned place preference tests [156].

These findings resonate with results observed in other social species. For example, degus reared in complete social isolation show increased risk-taking behaviors, altered sensitivity to rewarding stimuli, and social impairment during encounters with a stranger. Interestingly, no alteration of risk-taking behavior and hedonic responses were found in degus reared in partial isolation (individual housing plus daily 1-hr social interaction with peers). Thus, the availability of daily friendly interaction counteracted most of the behavioral changes induced by complete social isolation and served as a protective factor for emotional development [157].

Several human studies indicate that when the need to belong to a peer social group is not met, children show clear stress responses. For example, children experiencing rejection by classmates have enhanced cortisol levels [158]. In addition, peer victimization experiences, depressive symptoms, and evening cortisol levels are positively associated and predict later poor memory performance in preadolescents [159]. Lastly, socially helpless behavior is elevated in anxious solitary children, particularly those who habitually experience interpersonal stress in the form of peer exclusion [160]. Gazelle and Druhen [160] found that anxious, solitary, excluded children had excessive vagal suppression and elevated heart rate in response to a series of events involving peer behavioral rejection. It is not surprising that positive peer relations and peer acceptance, enhanced by social intervention programs, have a mediating role on children's externalizing behavior development [161]. Positive peer relationships also influence children's social information processing and self-evaluation. Specifically, shy/withdrawn children who have a close friend have less tendency to blame themselves for social difficulties [162]. As other studies have shown, the risk of peer-victimization and emotional problems is attenuated in children who have a close friend, indicating that friendship is a protective factor [163].

Positive social relationships may have beneficial effects for both the receiver and the provider of support. One salient prosocial feeling that drives us to interact with others in positive helpful ways is compassion. Compassion has been defined as both the feeling of warmth, understanding, and kindness that arises when witnessing the distress and suffering of others and a motivational state rooted in the evolutionarily preserved caring emotional system [164, 165]. Although compassion is triggered by negative and distressing antecedents, it generates positive outcomes. Notably, compassion is distinct from empathy. Empathizing with the suffering of others is associated with negative states, distress, and activations in brain networks that play a crucial role in empathy for pain. Conversely, compassion is accompanied by positive feelings of warmth and concern for the other and increased activation of brain networks related to reward and affiliation [166].

Evidence suggests that the experience of compassion may provide benefits to health and well-being over the long term [167, 168], due mostly to peripheral physiological changes associated with this emotional experience. Stellar and colleagues [169] showed that compassion is specifically associated with activation in the parasympathetic autonomic nervous system through the vagus nerve, with corresponding increased HRV. In their study, participants exhibited greater HRV during compassion induction compared, not only to a neutral control, but also to another positive emotion and another prosocial emotion lacking appraisals of another's

suffering. Their results suggest a specificity in the link between compassion and parasympathetic activity.

Promoting compassionate motivation and prosocial behavior has been shown to be beneficial for adolescents. Schreier and colleagues [170] conducted an experimental trial in which they assigned 106 high school students to either volunteering with elementary school-aged children for 2 months or a wait-list control group. While no group differences were found at baseline, at postintervention, adolescents in the intervention group showed significantly lower interleukin-6 levels, cholesterol levels, and body mass index compared with adolescents in the control group. Those in the intervention group who exhibited the greatest increases in compassion and altruistic behaviors also showed the greatest decreases in cardiovascular risk over time.

To our knowledge, human and animal studies of oxytocinergic influences on peer interactions in youth are missing. There are, however, studies on social interaction and vagal functioning in children (see [171] for a recent meta-analysis), which suggest that atypical HRV responses could be used to identify social dysfunction and psychopathology (*e.g.*, autism) and may be a useful marker of effective social regulation. Given the above-mentioned interrelationships between oxytocin and autonomic functioning, it is reasonable to hypothesize that oxytocin may facilitate peer interactions by modulating social salience perception and, in turn, social motivation and social approach. With respect to the opioidergic system, the few research groups working on peer interactions and opioids have demonstrated that endogenous opioids are important modulators of play activity in rats [17, 172-174]. The administration of opioid agonists, such as morphine, and antagonists, such as naloxone, are able to increase and decrease play activity, respectively [173-176].

In sum, studies in animals and humans suggest that positive peer relations play a crucial role in early affiliative bonds with group members and that endogenous opioids are important modulators of friendly social interactions. Studies of oxytocinergic influences on peer interactions in youth are warranted.

Positive Social Interactions in Adulthood

In adulthood, the availability of social support within romantic relationships, friendships, and extended social networks serves as protective factor for individual health. The "social buffering" effects extend from dampening HPA activation in response to stress [30, 177] to protection against cognitive impairment [178].

The presence of a companion regulates physiological responses to stress in animals and humans. For example, in sheep, the increase of cortisol levels induced by exposure to a novel anxiogenic environment is prevented by including a conspecific's picture in the novel environment [179]. Likewise, in rats, the odor of a conspecific—especially a familiar one—is able to mitigate stress responses during fear conditioning tests [180].

The oxytocin system is likely involved in the buffering effect of social companionship. Smith and Wang [181] observed the responses of female prairie voles exposed to acute immobilization stress and then allowed them to recover, either alone with oxytocin or placebo administration or paired with their male partner in conjunction with administration of oxytocin receptor antagonist or placebo. They found that, compared to the recovering alone condition, the companionship of the male partner in the placebo condition enhanced oxytocin levels in the paraventricular nucleus of the hypothalamus and prevented an increase in anxiety-like behaviors and circulating levels of corticosterone. In addition, while oxytocin injection decreased behavioral and corticosterone stress responses, oxytocin receptor antagonist administration counteracted the positive social buffering effects. Other researchers have shown that long-term peripheral administration of oxytocin can prevent the detrimental consequences of social isolation in female prairie voles [182, 183], such as depression-like behaviors, increased heart rate, reduced HRV, increased cardiac responsiveness to acute stressors, and disrupted sympathovagal balance [184].

The role of social support in reducing cortisol reactivity following acute stress and the involvement of the oxytocinergic system has also been reported in humans. For example, social support during exposure to verbal attack regarding a controversial issue counteracts the typical increase of cardiovascular reactivity [185]. Under acute social stress situations (*i.e.*, a public speech), support from a familiar person, such as a friend, attenuates cardiovascular reactivity to a greater degree than does support from an unfamiliar person [186]. In a similar stress situation, the presence of social support attenuates the increase of stress-induced cortisol levels [177]. A study by Heinrichs and colleagues [30] investigated the interaction between received social support and oxytocin administration in healthy men exposed to a standardized stress procedure, the Trier Social Stress Test. Before the stress procedure, participants received either oxytocin or placebo and were assigned to either receive or not receive social support from a best friend. Both oxytocin and social support were protective factors for preventing increases in cortisol responses, with participants receiving both oxytocin and social support having the lowest cortisol levels.

Kemp and colleagues [187] showed that oxytocin administration in healthy adults increases resting HRV, a crucial biomarker of approach-related motivation (*e.g.*, [188]) and an established risk factor for all-cause mortality [189]. However, lonely individuals prove to be less responsive to the salubrious effects of oxytocin on cardiovascular responsivity [31]. Again, the interconnections between oxytocin and autonomic nervous system functioning point to oxytocin as a key factor in explaining the protective effects of social support on cardiovascular risk.

Positive interactions not only contribute protecting against acute stress, they also ameliorate chronic stress conditions. While social isolation stress increases the likelihood of cardiovascular disorders [190], cognitive impairment [191], and ischemic stroke [192], social connection and social support protect against cardiovascular disease and cognitive aging [178, 193]. The latter also enhance recovery in chronic

disease conditions, such as cardiovascular and kidney diseases [194].

In humans, feelings of compassion, social connection, and positive affect toward others can be self-generated and increased using meditative practices [164]. Interestingly, these practices also train individuals to extend and direct positive feelings of compassion inwardly, toward the self, which becomes a recipient of one's own caring motivation [195]. Mindfulness meditation, which encompasses practices aimed to increase empathy, kindness, and compassion for self and others, has also been linked to telomere length, with considerable implications for neuroprotection [196]. A study of intensive daily meditation practice showed higher telomerase activity in individuals who participated in an intensive three-month full-time mediation retreat, compared to a wait-list control group [197]. Furthermore, beneficial effects of a mindful disposition, over a time span of two years, are characterized mostly by a non-judging and compassionate attitude toward our own thoughts and emotions [198]. Loving-kindness meditation (LKM), an exercise derived from contemplative Buddhist traditions and aimed at increasing "prosocial feelings" toward ourselves and others, has been shown to increase feelings of social connection toward unfamiliar individuals on both explicit and implicit levels [199]. This meditation practice has also been associated with longer telomeres in women [200]. Furthermore, research has found relationships between compassion meditation and reduced markers of inflammation. In one study, the amount of time spent in meditation was correlated with the reduction of C-reactive protein over 6 weeks [201]; in other work, individuals who performed more compassion meditation practice had lower interleukin-6 levels after a stress task that typically increases those levels, compared to the low-practice group [202]. Self-reported compassion was associated with activations in specific brain regions previously implicated in positive evaluation and affiliation [203]. Consistently, brief self-compassion training moderates biopsychological responses (alpha-amylase and HRV) to a social evaluative threat, such as the Trier Social Stress Test, in young women [204]. Similarly, self-compassion serves as a protective factor against stress-induced inflammation and inflammation-related disease. Participants higher in self-compassion exhibited significantly lower interleukin-6 after being exposed to a standardized laboratory stressor, as compared to less self-compassionate participants, even when controlling for self-esteem, depressive symptoms, demographic factors, and distress [205].

However, sensitivity to life adversity and to the positive effects of social support varies among individuals. For example, the beneficial effects of evoking social interactions through meditation and the facilitating role of oxytocin administration depend on an individual's attachment style and self-referential processing. Rockliff *et al*. [206] explored the effects of oxytocin on compassion-focused imagery (CFI)—that is, imagining another "mind" being deeply compassionate to oneself—and the interaction of these effects with self-criticism and feeling socially safe with others. Oxytocin increased the ease of imagining compassionate qualities; however, participants higher in self-criticism and lower in self-reassurance, social safeness, and attachment security had less-positive CFI experiences with oxytocin than with placebo, indicating that the effects of oxytocin on affiliation may depend on attachment and self-evaluative styles.

Possible factors involved in individual differences are also likely rooted in genetic differences. For example, studies on the single nucleotide polymorphism—rs53576 (G/A)—in the oxytocin receptor gene (*OXTR*) indicate that individuals with the G allele are more sensitive to social support during a standardized laboratory social stress test than are carriers of the A allele. Specifically, participants were assigned either to a positive supportive social interaction with a close friend or partner or to an alone condition prior to a Trier Social Stress Test. Individuals with one or two copies of the G allele and assigned to the social support condition had lower cortisol reactivity to stress than did individuals with the same genotype assigned to the alone condition. By contrast, no differences in cortisol levels were found between the social support and alone conditions among individuals with the A/A genotype [207]. Of note, when asked about their coping strategy in times of distress, individuals with the G genotype reported being more inclined to actively seek emotional social support than did carriers of the A allele [208]. Participants with the G genotype also had greater sensitivity to child behavior [209] and greater optimism and psychological resources compared to carriers of the A allele [210].

Likewise, natural genetic variations in opioid receptor genes are implicated in the expression of individual difference in sensitivity to social stress and to the beneficial effects of positive social interactions. In mice, the OPRM1 A118G SNP is associated with an increase in positive social interaction motivation. When exposed to acute social stress, that is, interactions with a resident aggressor, mice with the G allele showed less submissive behavior and more resilience to social defeat as well as greater c-Fos expression in the nucleus accumbens and periaqueductal gray [211].

In humans, individuals with the minor 118G allele of the OPRM1 report a high tendency to engage in close social relationships and experience social interactions as pleasant and rewarding, compared to carriers of the A allele [212]. When facing an acute social stress, such as a standardized laboratory social rejection task, carriers of the G allele show high sensitivity to social exclusion, as indicated by increased salivary cortisol levels and enhanced activation in dorsal anterior cingulated cortex and anterior insula, which are involved in social and physical pain processing [213].

The great sensitivity for social rejection among G carriers was confirmed in a Gene × Environment study in a clinical population. Within a heterogeneous group of individuals with psychiatric diagnosis, the carriers of the 118G allele had high fearful attachment scores, regardless of the reported quality of maternal care. However, the quality of maternal care was negatively correlated with fearful attachment scores in individuals with the A/A genotype [214].

Taken together, these studies stress the role of the oxytocinergic and opioidergic systems in sensitivity to social

distress and social reward, and they suggest that possible social neuroprotection interventions should take into account the differential susceptibility given by Gene × Environment interactions. Future studies should aim to further understanding of sensitivity to social interactions as a function of genotype by investigating the biomarkers associated with specific allelic variants. Given that individuals who perceive lower social support have shortened telomeres [54], especially in late life [215], it would be worth investigating whether specific genotypes associated with increased sensitivity to social interaction benefits on measures of cellular aging as well as neurogenesis after brain insults.

Notably, feedback mechanisms linking oxytocin and positive social exchanges play an important role not only in social bonding between humans but also in interspecies social bonding. Urinary oxytocin concentrations of dog owners were increased by the duration and intensity of their "dog's gaze" during a typical interaction. The authors suggested that interactions with dogs could increase the urinary oxytocin concentrations of their owners as a manifestation of attachment behavior [216]. Additionally, Nagasawa *et al*. [217] recently documented the existence of an interspecies oxytocin-mediated positive loop facilitated and modulated by gazing: dogs' gazing behavior, which reflects positive attachment, increased urinary oxytocin concentrations in owners, which consequently facilitated owners' affiliation and increased oxytocin concentration in the dogs. Nasally administered oxytocin increased dogs' gazing behavior, which in turn increased urinary oxytocin concentrations in owners. Similarly, tactile interaction between humans and dogs increased peripheral oxytocin concentrations in both [218]. Animal assisted activities could therefore be considered and tested as potential neuroprotective interventions, as already suggested by previous studies [219, 220].

In sum, these studies stress the role of the oxytocinergic and opioidergic systems in modulating the responsiveness to social stimuli and perception of their salience, and the relevance of Gene × Environment interactions.

Positive Social Interaction and Aging

Social factors assume a crucial importance in the well-being of elderly people due to the increased dependence on physical and social environments typical of this phase of life. Social support and integration, on the one hand, and social isolation and loneliness, on the other, as human existential conditions, are protective and risk factors, respectively, for physical and mental health throughout life, and they become more important in older people. In particular, social support and social integration profoundly influence older adults' health by reinforcing coping strategies and recovery [4, 221-223]. Consistently, Cacioppo *et al*. [224] found that loneliness predicted subsequent changes in depressive symptomatology, but not vice versa, in older adults. In recent epidemiological studies involving elderly people, lower social support was associated with increased illness severity and poorer treatment outcomes (see [225] and references therein), while greater social support and social cohesion at the neighborhood level were associated with reduced risk of mortality [226]. Social support in late life was also positively associated with leukocyte telomere length, an indicator of cellular aging [215]. Hawkley *et al*. [227] showed that higher initial levels of loneliness in elderly participants were associated with greater increases in systolic blood pressure over a 4-year period, independently of age, gender, race, ethnicity, medications, health conditions, and cardiovascular risk factors. Luo and colleagues [228] examined the relationship between loneliness, health, and mortality in a large population-based national sample of older Americans. Results showed that older adults with the highest levels of loneliness were 1.96 times more likely to die within six years than were those with the lowest levels of loneliness, even after controlling for sociodemographic characteristics and health behaviors. Although no studies directly investigated the physiological mechanism responsible for the relationship between loneliness and mortality in elderly adults, the previously described relationship between vagal tone, oxytocin, and increased health risk points to this critical pathway, especially in light of HRV's role in mortality risk for this population [229].

Carol Ryff [230, 231] provides an innovative and comprehensive psychosomatic biopsychosocial approach to health and illness, focusing on psychological well-being, to understand the neuroprotective role of positive interactions in elderly people. According to Ryff, well-being includes six dimensions (autonomy, self-acceptance, purpose in life, environmental mastery, positive relationships, and personal growth) that are involved in optimal aging and that may confer protection against illness and disease. The different dimensions of psychological well-being have social structural influences (*e.g.*, age, gender, socioeconomic status, race/ethnicity, and culture) and are linked with biological factors (*e.g.*, neuroendocrine regulation, inflammatory processes, and cardiovascular risk). Resilience ("the maintenance or recovery of health and well-being in the face of cumulative adversity") [231] is a key element of well-being and may be positively affected by social support through psychobiological mechanisms regulating stress response [232].

Social interactions and their effects on well-being and resilience rely on an individual's emotion processing of social stimuli. This is a central aspect in elderly people, given that longitudinal studies evidence that negative emotions decrease and positive emotions are stable or increase with age, and that anger control is greater in older adults than in younger adults [233-236]. Emotion expression and representation of close relationships may be altered in clinical conditions. For example, Farinelli and colleagues [237] explored the impact of brain lesions on attachment style and emotion expression and their relation with depression and anxiety in a group of elderly stroke patients. Negative basic emotions scores were higher for stroke patients than for a control group. That study also inferred different neuronal functioning for basic emotions and attachment in healthy brains, with alterations in emotion regulation, especially subcortical-cortical midline region activity [238], resulting from disrupted functioning due to brain lesions.

Anger expression in older adults predicts a higher prevalence of metabolic syndrome, which is considered a risk factor for cardio and cerebral vascular diseases [233]. In

addition, adults with greater anger in response to stressors exhibit greater production of proinflammatory cytokines [239], and those displaying more negative behavior during marital conflicts show enhanced endocrine activation and reduced immunological health in response to conflict [240]. These results are in line with the strength and vulnerability integration (SAVI) model [241], which indicates a reduction or even elimination of the typical "age-related advantages in emotional well-being" when under the effect of high arousal that activates stress reactions mediated by the HPA axis [232, 241]. Thus, the anger attenuation typical of aging may be considered protective for both organism and brain; indeed, because plasticity and flexibility of the biological system lessens with age, increased arousal can induce greater physical damage. In this context, positive relationships and social support, which have a role in social buffering effects [232], may assume a crucial role in attenuating dysfunctional responses to stress and in promoting neuroprotection by enhancing resilience and reducing diseases, including cerebrovascular diseases [242, 243].

Attachment strategies play a key role in influencing emotion expression and emotion regulation mechanisms. However, only a few studies have explored attachment in elderly people [244-246]. Among these, Cicirelli [244] found that elderly people have fewer attachment figures than do youths, and those attachment figures include adult children, deceased loved ones, and God; he suggested that attachment figures are critical for optimal adaptation and well-being in elderly people. Of note, meditation that includes imagery of positive social interactions has a neuroprotective effect against brain aging. For example, meditators show a lack of age-related atrophy of brain grey matter [247]. In another longitudinal study, older adults were taught meditation or given music to listen to. The meditation group had a greater rise in telomerase activity compared to the group who listened to music [248]. A small randomized-control trial has shown that the mindfulness-based stress reduction (MBSR) meditation program reduced loneliness and proinflammatory gene expression in older adults. It is known that lonely older adults have increased expression of proinflammatory genes as well as increased risk for morbidity and mortality [249]. Eight-weeks of MBSR was found to reduce loneliness and to downregulate proinflammatory NF-κB-related gene expression in circulating leukocytes. Thus, MBSR techniques, which naturally include components of compassion [250] and augment self-compassion [251], may be a valuable neuro-protective intervention for elderly people.

Human and animal studies have revealed the complex interaction of neuromodulators with the neuroprotective functions involved in attachment, social support and positive interactions, social buffering effect in stress response regulation, and plastic reparative and adaptive phenomena following trauma and brain lesions in adults. Despite this large body of literature, the study of opioid's and oxytocin's role in elderly people is still scarce. Indirect evidence of the opioid system's neuroprotective role in elderly people may be inferred from multiple alterations in the opioid receptors found in Alzheimer's disease, which is the most common degenerative disease in elderly people and is associated with dementia [252, 253]. In particular, opioidergic system dysfunction may be involved in the pathogenesis of Alzheimer's dementia by dysregulating the neurotransmitters acetylcholine, norepinephrine, serotonin, GABA, and glutamate [253].

Alterations of the oxytocinergic system are likely involved in manifestations of neurodegenerative diseases with presenile onset, such as behavioral frontotemporal dementia (bvFTD), which is characterized by disturbances in social cognition, interpersonal behavior, and emotional blunting. The brain areas and behaviors affected by bvFTD partially overlap with the oxytocinergic system. A pioneering study of oxytocin's effects on dementia symptoms shows that a single dose of oxytocin administration improves Neuropsychiatric Inventory scores and reduces recognition of angry facial expressions in patients with bvFTD [254], presumably by improving self-confidence [29, 132].

The oxytocinergic system, with its interactions with the reward-seeking dopaminergic system, is also presumably involved in emotional alterations found in stroke patients. Elderly patients with stroke reported increased depression and reduced "seeking" behaviors [255]—a dopaminergic-mediated positive basic emotion that supports exploratory behaviors and social approach and energizes other basic emotional systems [73].

Animal models of human stroke indicate that oxytocin plays a crucial mediating role in the neuroprotective effects of social interaction on stroke outcomes. In a study by Karelina *et al*. [243], adult male mice were socially isolated or socially housed prior to induction of an experimental stroke. Social interaction increased hypothalamic oxytocin gene expression, and socially housed mice showed attenuated infarct size, neuroinflammation, and oxidative stress following experimental stroke. The neuroprotective effects of social interaction were completely eliminated by oxytocin receptor antagonist treatment. Oxytocin administration in socially isolated mice reproduced the neuroprotection conferred by social housing. In the same study, oxytocin also directly suppressed cultured microglia, which are key instigators in the development of neuroinflammation after cerebral ischemia. Taken together, animal and human studies suggest that social interaction, mediated by oxytocin, provides neuroprotective effects for poststroke recovery and outcome [226, 243]. Further studies of opioidergic system dysfunction in dementia in elderly people are needed.

SUMMARY AND FUTURE DIRECTIONS

Positive social interactions play a key role in neuroprotection throughout life by promoting healthy neurodevelopment and counteracting brain aging in adulthood, protecting brains in elderly people, and facilitating recovery after brain insult. During the prenatal period, a positive social environment contributes to regulating maternal HPA activation and protecting the fetus from exposure to maternal high glucocorticoid levels [40]. On the other hand, exposure to excessive psychosocial maternal stress during the prenatal period leads to a series of risk factors for psychological and physical diseases. Possible adverse effects may be significantly reduced by postnatal social neuroprotection interventions involving caregiver–

infant physical contact (*e.g.*, massage therapy) [86]. Neuroprotection programs imply the activation of oxytocinergic and opioidergic systems and determine the development of future social and emotion regulations skills, likely *via* action on the vagal nerve, an integrative biomarker for biological (*e.g.*, immune dysfunction and inflammation) and psychological (*e.g.*, emotion regulation) functioning [34].

Throughout development, positive social contact with the caregiver acts as a "hidden regulator" and promotes infant neuroaffective development. During childhood and adolescence, social support has an important role in blunting physiological reactivity to stressors, protecting against the development of psychopathological diseases such as depression, and reducing pain perception, even in chronic pain sufferers [256]. Attachment figures and friendships in adulthood continue to have a protective role for individual health and brain functioning to the point that social networks are key contributors to cognitive reserve, that is, the ability to tolerate age-related changes and disease-related pathology in the brain without developing clear clinical symptoms or signs (cognitive reserve hypothesis) [257]. Interestingly, positive relationships based on social support may be beneficial for both the receiver and the provider of support. Compassion, characterized by feelings of caring, has been found to provide benefits to health and well-being over the long term [167, 168]. These benefits are likely due to activation of the parasympathetic autonomic nervous system, and an associated increased HRV, which is linked to the emotional state of compassion [169].

As human and animal studies suggest, the oxytocinergic and opioidergic systems are important mediators of the effects of social interactions. Administration of oxytocin modulates social motivation and regulates physiological reactivity to stressors in both humans and animals [29, 31]. Results from the examined studies were mostly consistent. However, several caveats must be acknowledged: (1) most of the reported human studies are correlational; (2) interpretation of results from studies that focused on plasma and urine oxytocin levels are controversial because peripheral oxytocin levels are not always associated with central oxytocin levels; (3) most of the studies focus on a specific phase of life (*i.e.*, adulthood); and (4) studies of sex differences in opioid and oxytocin sensitivity are scarce.

Future studies should focus on the role of opioids and oxytocin in social interactions as a function of social experiences throughout life. Along with [232], our work highlights the need for a developmental perspective regarding the psychobiological foundation of social support. In fact, even though evidence exists for social support's neuroprotective role from gestation to late life, it is unclear if that neuroprotective role varies as a function of age. Additionally, assessment of multiple physiological markers of neuroprotection is likely to increase the robustness of findings; therefore, such assessment should be the aim of future studies. For example, despite the critical interrelationships between oxytocin and vagal functioning, studies assessing both markers are few. This is a serious limitation in light of Quintana *et al.*'s [258] claim that vagally-mediated HRV may provide a marker of response to oxytocin treatment that could be used to predict who might respond favorably to oxytocin administration, which could result in improved social capacity in humans.

With these cautions in mind, the present work may inform the development of ad hoc neuroprotection interventions focused on social support to promote well-being, enhance resilience, and reduce psychological and physical suffering. Among these, practices that enhance feelings of compassion, social connection, and positive affects toward others and the self, such as compassion focused therapy [164], should be further tested for their efficacy in influencing markers of neuroprotection throughout life.

The studies we reviewed in this paper suggest the involvement of the opioidergic and oxytocinergic systems in the perception of self and others in healthy conditions [259-261] and in the onset or persistence of several disorders. For example, alterations of these systems may be central in disorders characterized by impaired social bond formation (*e.g.*, social anxiety and autism), emotion recognition (*e.g.*, alexythimia), and mood disorders associated with brain aging.

In addition, future research should focus on the psychobiological foundation of the large variety of technical interventions available in psychological clinical science and practice, to further the understanding of crucial factors involved in the efficacy of psychotherapy [262]. Given the limited information available on oxytocin [263] and opioid [264] involvement in placebo analgesia effects and given the key role of physician–patient interactions in therapeutic outcomes [265, 266], future studies should explore whether and to what extent the oxytocinergic and opioidergic systems mediate the quality of physician-patient relationships, with associated implications for social neuroprotection interventions. Furthermore, the role of the oxytocinergic and opioidergic systems in expression of the individual's personality within family, larger social systems and relational matrix should be systematically investigated in clinical research and unified psychotherapy. Psychological intervention may represent a potential and effective source of positive interactions and neuroprotection improving health, and subjective well-being.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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