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The neurobiological link between compassion and love

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Summary

Love and compassion exert pleasant feelings and rewarding effects. Besides their emotional role and capacity to govern behavior, appetitive motivation, and a general 'positive state', even 'spiritual' at times, the behaviors shown in love and compassion clearly rely on neurobiological mechanisms and underlying molecular principles. These processes and pathways involve the brain's limbic motivation and reward circuits, that is, a finely tuned and profound autoregulation. This capacity to self-regulate emotions, approach behaviors and even pair bonding, as well as social contact in general, i.e., love, attachment and compassion, can be highly effective in stress reduction, survival and overall health. Yet, molecular biology is the basis of interpersonal neurobiology, however, there is no answer to the question of what comes first or is more important: It is a cybernetic capacity and complex circuit of autoregulation that is clearly 'amazing'.

key words: **interpersonal neurobiology • love • compassion • spirituality • autoregulation • stress • motivation • reward • morphine • dopamine • oxytocin**

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Background

Charles Darwin and other biological scientists that have examined the biological evolution and its basic principles found various mechanisms that steer behavior and biological development. Besides their theory on the natural selection, it was particularly the sexual selection process that gained significance in the latter context over the last century, especially when it comes to the question of what makes us 'what we are', i.e., human. However, the capacity to sexually select and evolve is not at all a human accomplishment alone, or sign for uniqueness; yet, we humans, as it seems, are especially smart in fooling ourselves and others – when we are in love or desperately search for it.

Biological behaviorism always tried to elucidate what governs or steers animal and human behavior and appetence processes. Various theories of behavioral control and motivation formation evolved, to the point of the stages of change, or transtheoretical, model of the social biological sciences and sociology. Today, modern neurobiology and its diverse instruments and highly developed experimental techniques help to better understand the biological roots and core mechanisms of interest for behavior research and analysis. In complementing the biological and social approaches, neurobiology, and brain research, came to aid for a deeper knowledge and understanding. Interestingly, it were biologists and basic (neuro-) scientists that found some of the molecular key players involved in the nervous system that steer behavior and autoregulation [1]. Now it is almost a common understanding that the brain is the central organ of behavior regulation. And it is so in love and compassion processes, likewise.

Love is defined in the Oxford English Dictionary as an intense feeling of deep affection or fondness for a person or a thing, a sexual passion, or sexual relations, in general. Thus, love is an emotion often associated with consensual sexual activity, or the willing, and even eager, participation of the individuals involved [2]. Medical, or health, implications of love are still speculative and neurobiological research has only started to examine the possible mechanisms underlying this assumption and its consequences for the individual organism and associated ontogenetic health outcomes and benefits [2–6].

Attachment, commitment, intimacy, passion, grief upon separation, and jealousy are but a few of the emotionally-loaded terms used to describe that which love represents [3,7,8]. In science, however, love appears to be a hypothetical and multi-dimensional construct with many interpretations and implications [3,4]. Love and its various emotional states and behaviors are rarely investigated by scientific means. Emotions and feelings such as attachment, couple and parental bonding, and even love have now come into the focus of neuroscientific research [9]. Thus, knowledge on the neurobiology of love has yet to evolve, and only recently, exciting research has brought to surface detailed information on molecular and physiological "ingredients" of the love phenomenon, as described later on. The concept of love also involves having an emotional bond to someone for whom one yearns [10]. Thus, the psychological sense of love can be interpreted as referring to the satisfaction of a yearning, which may be associated with the obtaining of certain sensory stimulation [10]. Love therefore possesses a close connection not only with reward and pleasure phenomena, but also with appetitive and addictive behaviors [4,6,11,12].

Compassion, in completion, represents a human behavioral quality, which can be considered emotional in nature, which allows us to express empathy and sympathy. Intellectually, it allows us to embrace another human's suffering with an emotional bond of support. In this regard it is coupled to attachment and a "love" link in all probability utilizing similar physiological and biochemical substrate for its manifestation, i.e., reward processes, since it allows the giver a rewarding experience by extending oneself. However, in this act of altruism or kindness, here too, a stress may be present in that the receiver may not want compassion (sympathy). Thus, like love, a stress associated anticipatory stress response is potentially present [13]. In addition, compassion, and especially empathy, not only secure contact and one's own stress modulation, but also make a connection between individuals before, or besides, a loving or caring relationship. This quality, that relies on the biological capacity to make contact, support and be supported, and connect, is a core ability of behavior and human neurobiology, and this is not only due to the fact that the down-stream cognitive functions, e.g. 'theory of mind', are represented within the brain, but particularly the bottom-up processes, i.e., emotional perspective taking or mirror neuron system activity.

Behavioral Processes

Naturally rewarding activities like love boost a flood of stimulating signaling molecules [4,11,14,15]. However, this stimulation may not be as strong or enduring as that achievable by addictive drugs – natural rewards may not, like some artificial drugs, completely surpass normal physiology and feedback since these are administered at higher doses [11,16–19]. Addictive drugs immediately build up high appetence levels that are not released completely or only for a short time after consumption [20–22]. This frustrating fact produces even more appetence: One cannot stop the pleasure-seeking activity that now starts to control normal behaviors (i.e., motivational toxicity) [11]. While natural activities are controlled by feedback mechanisms that activate aversive centers (i.e., aversive motivation), no such restrictions bind the responses to artificial stimuli [23,24]. Thus, love and addiction are evolutionarily and behaviorally interconnected, but they are not the same, at least not in relation to artificial drug ingestion. Being "addicted to love", however, refers to this interconnection.

Love and stress

Love, e.g., when experiencing symptoms such as sweating, heart beat acceleration, increased bowel peristalsis and even diarrhea, can be quite a stressful experience. However, love is certainly known, primarily, for its relation to feelings that we usually like to experience. This intense sensational and emotional state has inspired artists, and therefore, biologists have concluded that art, when it is associated with biological phenomena like love and reproduction, is part of an adaptational process ensuring survival [25–29]. Hence, love or lust, and the joy that is imbedded in the love concept, seem to be not only individually rewarding but also

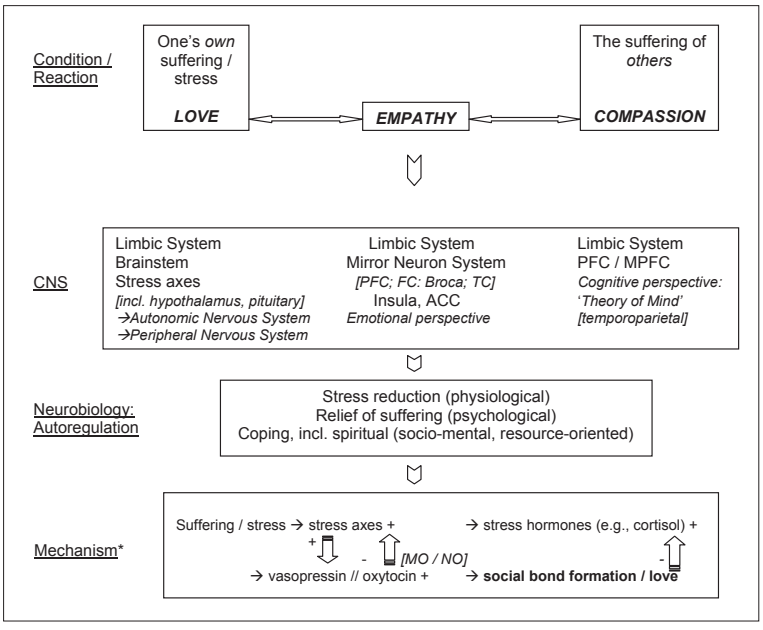

Figure 1. The neurobiological regulation of stress or suffering via love and compassion. Explanations and references see text. Abbreviations (as used in the figure): CNS – central nervous system; PFC – prefrontal cortex; FC – frontal cortex; ACC – anterior cingulate cortex; TC – temporal cortex; MPFC – medial prefrontal cortex; MO – endogenous morphine; NO – nitric oxide. * Note: Stress induces hypothalamic and pituitary activation, i.e., stress axes/stress response induction (stress hormone release) and a potentially direct – as well as indirect – induction of vasopressin and oxytocin release (bonding hormones), which are then binding, e.g., in the brainstem; the initial stress physiology, that is, a state of arousal/alertness, is thus counteracted by oxytocin, e.g., via morphine and a subsequent nitric oxide release, on the molecular/receptor level; as a result, social bond formation, positive social motivation, attachment and interaction get enhanced, i.e., love and compassion, which – via limbic reward and motivation circuits and the underlying signaling systems – enhance feelings of safety and well-being, and reduce anxiety, stress, tension and constraint; clearly, CNS morphology and function, autoregulation and neurobiology and attachment behaviors are strongly interconnected.

behaviorally and biologically advantageous experiences, thereby protecting the species [11,25,30]. Questions like these have recently become a focus of evolutionary psychology, a field of sociobiology [25], again demonstrating the integrative character of love research.

In recent reviews on the role of stress in human attachment, it has been discussed that stressors can trigger a search for pleasure, proximity and closeness, i.e., attachment behaviors, thereby promoting the re-balancing of altered physiological and psychological states [11,31,31]. Forced isolation, anxiety, fear, and other forms of stress are associated with increased levels of stress hormones like cortisol, i.e., enhanced hypothalamic-pituitary-adrenal (HPA) axis activity [3,32,33]. Such conditions or experiences normally tend to encourage social interactions (Figure 1). However, excessive stress (i.e., chronic) that could compromise health and survival, e.g., (hyper)intense grief, may lead to depression or the breakdown of social relationships [33,34]. Within a homeostatic range, stress-related physiological processes, including hormones of the HPA axis, can promote the development of social bonding [35]. In addition, positive social interactions may help to create physiological states that are anxiolytic and stress reducing, i.e., health promoting [3,14,36,37]. Thus, balance is a key concept in social bonding and love, including related neurobiology (see below).

Feelings of security and support lead to the facilitation of trust and belief, including "meaning and spirituality," thereby inducing positive motivation and behavior [11,38,39]. In species that form heterosexual pairs, rewarding sexual activities are associated with the formation of social attachments and bonds [40]. Sexual behavior, however, can also be physiologically stressful for both sexes [3], as described earlier. Adrenal steroids, vasopressin, oxytocin, dopamine, and endogenous opioids as well as opiates and higher levels/pulses of nitric oxide (NO) are released during pleasurable activities like sexual behaviors (e.g., 'making love') [11,14,41–46], indicating neurobiological pathways that are linked to stress response and reward mechanisms likewise.

Within the context of varying stimuli evoking NO release, emotional stresses such as fear and anxiety can induce cardiovascular alterations, such as cardiac arrhythmia [43]. Cardiovascular events are initiated at the level of cingulated, amygdalar, and hypothalamic central nervous system (CNS) processes, as well as their projections into higher level cerebral cortex, further altering heart rate under stressful or sexually aroused conditions [47]. Neurons in the insular cortex, the central nucleus of the amygdala, and the lateral hypothalamus, owing to their role in the integration of emotional and ambient sensory input, may be involved in the emotional link to the cardiovascular phenomena [48]. These include changes in cardiac autonomic tone, with a shift from the cardioprotective effects of parasympathetic predominance to massive cardiac sympathetic activation [49]. This autonomic component, carried out with parasympathetic and sympathetic preganglionic cells via subcortical nuclei from which descending central autonomic pathways arise, may, therefore, be a major pathway in how emotional states may affect cardiovascular function and health [41,43].

Furthermore, oxytocin, a major player in love physiology, has also been associated with stress reduction [3]. In humans [50–53], oxytocin inhibits sympathoadrenal and stress response activity, including the release of adrenal corticoids

(Figure 1). In addition, subjects in love show higher cortisol levels as compared with those not experiencing this state [54]. This condition of love-related hypercortisolemia may represent a non-specific indicator of changes that occur during the early phase of a relationship, thereby reflecting the somewhat stressful condition or a general arousal associated with the initiation of social contact [13,54]. This physiological state of alertness [13], associated with love, may help to overcome neophobia, although this is still a speculative aspect [54]. Such positive stress appears to be important for the formation of social contact and attachment, since a moderate level of stress has been demonstrated to promote this kind of relationship, i.e., social bonding [3,35,54–58]. Oxytocin, as it seems, really illustrates the dynamic autoregulation involved in love and deep relationships: It is part of the 'chill experience' in the initial phase or the arousal of loving encounters and treatments, but simultaneously reduces stress on the psychological level (e.g., via bond formation) and on the physiological level (e.g., via stress hormone inhibition, opiate-like effects and/or NO release) [2–4,7,34,44]. Thus, love seems to be a complex phenomenon and, with regard to stress, an ambiguous experience, i.e., double-edged sword.

Motivation and behavior

Motivation concerns aspects of intention or activation [11]. Consequently, it lies at the core of biological, cognitive and social regulation [59]. Motivation is highly valued in health care since it produces behavioral changes or adjustments and can mobilize others to act [59]. A large amount of behavior can be explained by simple processes of approaching pleasant and avoiding painful stimuli [13,60]. Reward and punishment are functionally and anatomically interconnected [11]. A crucial component of CNS reward and motivation circuitries, as they are steering behavior, are nerve cells that originate in the ventral tegmental area (VTA), near the base of the brain [11]. These cells send projections to target regions in the frontal brain, most notably to a structure deep beneath the frontal cortex, i.e., nucleus accumbens (part of the 'ventral striatum') [20,21]. The essential neurotransmitter of this connection is dopamine. Clearly, the VTA or the mesolimbic dopamine system represents a rather old, but very effective, part of motivational physiology and behavior [11]. However, in mammals (humans), the neurobiology of behavior, including reward circuit involvement, is far more complex, and it is integrated with several other brain regions that serve to enrich an experience with emotion, as an example. In addition, these brain regions also direct the individual's response or actual behaviors toward rewarding stimuli, including food, sex and social interaction [61]. For example, the amygdala helps to assess whether an experience is pleasurable or aversive (and whether it should be repeated or avoided) and further helps to forge connections between an experience and other cues, particularly emotional [20,21]. The hippocampus participates in recording memories of an experience, including where, when, and with whom it occurred [61]. The frontal cortex, however, coordinates and processes all information and consequently determines and executes the ultimate behavior [11]. Finally, the VTA-accumbens pathway acts as a measuring tool and regulator of reward: it tells the other brain centers how rewarding an activity is or was [61]. The more rewarding an activity is deemed, the more likely the individual is to remember and repeat it [61].

Limbic functions: Reward and pleasure

The biological mechanism mediating behavior motivated by events commonly associated with pleasure is called 'reward' [4,11,12]. It is usually governing normal behavior through pleasurable experiences [23]. Pleasure, however, describes a 'state or feeling of happiness or satisfaction resulting from an experience that one enjoys' [62]. Pleasure is a subjective phenomenon, i.e., subjective quality. It is the 'good feeling' that comes from satisfying homeostatic needs such as hunger, sex, and bodily comfort [11]. Hence, an intimate association between reward and pleasure exists [23,61]. In neurobiology, pleasure is a competence or function of the reward and motivation circuitries that are imbedded in the CNS. Anatomically, these reward pathways are particularly linked to the brain's limbic system [11,14,28,32,33,63].

Love has the capacity to influence the autonomic-emotional integration system, i.e., limbic system [14,64]. Here, the autonomic nervous system (ANS) and emotions are wired together. Furthermore, sympathetic activity and stress hormone production are imbedded in underlying autoregulatory circuits [28,33,37]. An association of love with emotions, neurotransmitter and stress hormone production (Figure 1), autonomic responses, behavior, and mood states becomes obvious [14]. The influence of love on vital functions such as breath, respiratory rate, blood pressure, and cardiac output, as a result of the autonomic-emotional integration, can lead to a different consciousness, or altered state of mind, when in love [14,65]. Hence, the activation of the brain's reward system produces changes ranging from slight mood elevation to intense pleasure and euphoria, and these physiological states usually help to direct behavior towards natural rewards, e.g., love [11,66–69].

Neurobiologists have long known that the euphoria induced by drugs of abuse, sex, or other things we enjoy, arises because all these factors ultimately boost the activity of the brain's reward systems [11]. These are made up of complex circuits of nerve cells that evolved to make us feel flush after eating or sex – things we need to do to survive and pass along our genes [20,21]. Reward pathways are evolutionarily ancient like limbic structures. In fact, these pathways are essentially of limbic origin [11,14]. For example, prefrontal or orbitofrontal cortices, cingulate gyrus, amygdala, hippocampus, and nucleus accumbens participate in the reward physiology [41]. The lateral orbitofrontal cortex, for instance, is activated with pleasant visual, tactile, or olfactory stimuli, with its response depending on pleasantness rather than intensity of stimulation [70–73]. Memories of the pleasure of wellness, i.e., "remembered wellness," are accessible to this system through hippocampal mechanisms [14]. With regard to frequent CNS reward "tracks," activation of the medial forebrain bundle (MFB), as it courses through the lateral hypothalamus to the ventral tegmentum, has been shown to produce robust rewarding effects [23,74]. Important neurotransmitters here are serotonin and dopamine [11,75]. Electrophysiological and neurochemical techniques revealed that CNS stimulation can activate a descending component of the MFB which is synaptically coupled at the ventral tegmentum to the ascending mesolimbic dopamine system, i.e., nucleus accumbens [11,23,61,74–76]. Thus, pleasure induction involves a circuitous reward pathway, first activating a descending MFB

component and then, as described, the ascending mesolimbic dopamine pathway.

Psychomotor stimulants, opiates, and natural rewards like food and sex, seem to predominantly activate the reward pathways by their molecular or pharmacological actions in the VTA and nucleus accumbens, as well as amygdala and other related structures, i.e., mesolimbic or frontal/prefrontal areas [11,20,21,76,77]. Ventral tegmental activation, as described, involves dopamine signaling [11]. Other neurotransmitters (e.g., GABA, glutamate, serotonin, the stress hormones noradrenalin and cortisol, as well as acetylcholine, NO, endorphins/opioid peptides, and endocannabinoids) also play a critical role in reward physiology [11,63,78]. In addition, endogenous morphine/opiate production may be of critical importance [11,14,29,42,43,79,80]. Hence, research has only begun to elucidate the specific underlying molecular pathways and neurobiological key players of human motivation or reward circuitry and behavior.

Feeding, maternal behavior, or sexual activity can each be facilitated by opiate activation of the reward system [77]. The origin of the VTA (i.e., the VTA dopamine system) seems to provide an important neurochemical interface where opiates and opioid peptides of exogenous or endogenous origin can activate a CNS mechanism involved in appetitive motivation and reward [14,23]. Obviously, endogenous morphinergic signaling plays a significant role here [11,14]. This is especially true since endogenous morphine biosynthesis, found in humans, vertebrates, mammals, and invertebrates [14,42,43,81], involves elements of dopamine synthesis and its metabolism [11,14,82–85], thereby linking two critical signaling systems [86,87]. Specifically, endogenous morphine production has been demonstrated in limbic tissues, e.g., hippocampus and amygdala [42,43,88,89]. It is made by human and invertebrate cells [90,91] and dopamine serves as a major precursor, linking many of these phenomena (love, addiction, eating) into a "common" signaling family [87,92]. It's presence in human stem cells underscores its importance in evolution as well as its persistence [92,93]. Morphinergic signaling has further been found to release constitutive NO [94], thus linking endogenous morphine and NO to limbic reward and pleasure pathways [11]. Taken together, limbic areas are functionally and molecularly connected to the frontal/prefrontal cortex which integrates emotion, memory, belief, expectation, motivation and reward processing, i.e., affective and motivational responses [41,95]. Also, prefrontal mechanisms may trigger dopamine, NO, and opiate release in the midbrain [96]. After all, the VTA serves as an appetitive motivation system for diverse behaviors, including sex, since it controls both normal and pathological behaviors [14,23,67,76]. Compassion also belongs into this sequence of basic human behaviors since it (stemming from the Latin word for 'co-suffering') is a 'virtue' – one in which the emotional capacities of empathy and sympathy, e.g., for the suffering of others, are regarded as a cornerstone of greater social interconnectedness and humanism (Figure 1). However, the biological root probably is not humanism for its own sake but that people in need, and their knowledge and competencies, and even genes, are secured and cared for – and preserved. Behaviors and molecules are biologically supplied to ensure these protective activities, for the sake of the species and the individuals involved.

Based on the known functions of the catecholamines, e.g., norepinephrine and dopamine, it is likely that catecholamines are involved in pair bond formation, as shown above [3]. Dopamine agonists, capable of inducing reward and pleasure, release oxytocin, and interactions between oxytocin and dopamine have been reported in rats, also in humans, recently [97,98]. Additionally, high levels of oxytocin receptor activity have been demonstrated in the nucleus accumbens of prairie voles [99], which is "equipped" with intense dopamine signaling (see above). Given the link between dopamine and endogenous morphine via common precursors, we surmise morphine's involvement here as well [85–87,92,100,101]. Also, in the mammalian brainstem, e.g., raphe area, where we find serotoninergic target neurons, a substantial oxytocin and morphine signaling and their mutual influence is evident [14,82,100]. Again, serotoninergic and oxytocinergic signaling (as well as morphinergic) include bonding or pleasurable and rewarding experiences and anxiolysis, i.e., decreased aggressiveness and increased compassion and 'happiness'. Interactions between oxytocin and catecholamines may therefore provide a mechanism for rewarding or reinforcing pair bonding [3]. Furthermore, catecholamines may be necessary to activate or reward various behaviors, including arousal and selective attention, and may also regulate the effects of oxytocin and vasopressin in the CNS [3,102]. Taken together, it seems plausible that pleasurable sensations produced by sexual activities would provide mechanisms that reinforce behavior, thereby promoting its repetition [43]. In the context of adaptive behavior and its necessity in evolution, it would appear that the pleasure generated by sexual stimulation, orgasm or intercourse would be selected-for evolutionarily [43]. Consequently, pleasure can be seen as an effective and important adaptive mechanism, the function of which is to ensure the procreation and survival of a species [11,43].

The Neurophysiology of Love

Findings related to oxytocin and vasopressin research and connected neurobiological aspects including the role of monoamines and other peptides like endogenous opioids suggest a tight coupling between attachment processes, love phenomena, and reward pathways, i.e., lust, happiness, pleasure, passion, compassion and desire [11,54,70,103,104]. In fact, most regions charted to contain vasopressin and oxytocin receptors in the human brain are activated by both maternal and romantic love [70,105,106]. Interestingly, the same neurohormones are involved in the attachment between mother and child (in both directions, see above) and in the long-term pair bonding between adults, although each neurohormone has distinct binding sites (though overlapping, see below) and may further possess its own gender-specificity [70,107].

Oxytocin and vasopressin receptors have been found, for example, in the olfactory and limbic-hypothalamic systems, as well as in brainstem and spinal cord areas that regulate reproductive and autonomic functions [3]. However, the distributions of these receptors within the CNS vary across development and among mammalian species [108–115]. The specific patterns and densities of oxytocin binding sites may also be influenced by steroid hormones, including estrogen, progesterone, androgens, and glucocorticoids (Figure 1).

Moreover, developmental hormonal experiences may alter adult gene expression for both oxytocin and vasopressin receptors [3,116]. The capacity of peptides to respond to developmental processes may thus provide a mechanism through which individual ontogenetic experiences can influence adult social behavior. However, oxytocin and vasopressin are capable of binding to each other's receptors [109], a fact that is further complicating the analyses of pathways through which oxytocin and vasopressin affect social attachment behaviors [3]. In addition, catecholamines, endogenous opioids, and prolactin influence parental behavior as well, either by modulating the rewarding aspects of this behavior [117,118], pacing mother-infant interactions [119], or through their documented abilities to affect the release and actions of other peptides, including oxytocin [3,120]. Finally, release patterns of both neuropeptides vary since oxytocin appears to act faster and with more dramatic pulses, as compared to vasopressin [121].

The early phase of love may represent a rather extreme neurobiological state, even physiologically contradictory to subsequent phases and states. Within the brain, testosterone receptors are distributed, for example, around hypothalamic regions where testosterone eventually is aromatized – i.e., processed – into estrogens, which then appear to determine an actual increase in aggressiveness [122]. However, the specific pathways involved as well as the significance of related estrogen signaling are still speculative. A behavioral correlation between testosterone and serotonin levels has also been demonstrated. In fact, a lack or diminution of CNS serotonin contents apparently increases aggressive behaviors both in animals and humans [122]. Moreover, testosterone further enhances vasopressin levels in the medial amygdala, lateral hypothalamus, and the preoptical medial area, involved in aggressive behaviors [122]. Thus, gonadal or sex hormones are involved in the neurophysiology of love, not surprisingly: Gonadal steroids, including androgens and estrogen, may exert developmental effects on neural systems that have been implicated in social attachment, and they may mediate both genetic and environmental influences on the propensity to love and form attachments [3]. These hormones may further regulate oxytocinergic or vasopressinergic functions, as well as the expression of other peptides and neurotransmitters, which in turn can also modulate oxytocin and vasopressin, i.e., autoregulatory feedback [3]. However, social attachment apparently occurs even in the absence of gonadal steroids, pointing out their questionable role within the framework of love and social attachment. Again, we see the complex interrelations of molecular signaling processes underlying love phenomena and sex-related behaviors.

Dopamine has recently received special attention from psychopharmacologists and neurobiologists due to its obvious role not only in the placebo physiology, but also in mood, affect, and motivation regulation [11,23,76,123]. Clearly, dopamine plays a significant role in love phenomena and related physiology, especially in the beginning, and even some of the peripheral aspects or symptoms associated with love – e.g., increased intestinal peristalsis and diarrhea, as described – may represent consequences of intense dopamine signaling involved in the love physiology. However, with this report we primarily focus upon the neurobiological features of love-related dopamine release, especially within the CNS: Although several distinct dopamine systems (i.e., receptors and their subtypes) exist in the brain, the mesolimbic dopamine system appears to be the most important for motivational processes [23,124]. Hence, the quantitatively most important dopamine receptors in the brain, i.e., D1 and D2, though partially functional antagonists, are both significantly expressed in the nucleus accumbens tissue. In addition, the other dopamine receptors (D3-5) are also linked to the limbic system, with regard to their neurobiological role in the CNS, in particular with reference to their substantial existence in amygdalar and the hippocampal tissues. They all seem to work on the reward and motivation physiology and may have a common regulatory and evolutionary root, since their functions biologically overlap and their molecular ground plan still reveals a high sequence homology. Accordingly, dopamine, interpreted here as a critical part of the biologically important reward process, is a central instrument for the neurobiology of love. This seems to be particularly true with regard to the stimulating and pleasurable aspects of dopamine signaling [11]. It is important to note that, based on new knowledge, there is a potential for endogenous morphine signaling to be part of this process [79,80,86,100,125,126].

Endogenous morphine, both biochemically and immunocytochemically, has been found in various neural tissues, including limbic structures [16,83,88,127–134]. These same structures, interestingly, exhibit vasopressinergic or oxytocinergic signaling, i.e., amygdala, nucleus accumbens, periaqueductal grey, raphe nucleus, VTA, hippocampus, etc., which, again, indicates a close relationship of both signaling systems with the limbic reward concept [9,54,135]. Additionally, reports demonstrate the presence of morphine precursors in various mammalian tissues, including brain [14]. Furthermore, an opiate receptor subtype, designated mu3, has been cloned, which is opiate alkaloid selective and opioid peptide insensitive [136], strongly supporting the hypothesis of an endogenous morphinergic signaling system [11,14,42,43,81]. The psychiatric implications of this system have been examined, including brain reward circuitry [79]. Morphine, given its reported effects and those exerted via constitutive NO release [11,42,43,137,138], may thus form the foundation of a common signaling among love and pleasure phenomena, including attachment behaviors and compassion [11,14,70,139].

Common CNS pathways: Love and Other Rewarding Experiences

The profound neurophysiological and neurobiological connection between love and reward has become obvious. Hence, the limbic reward and motivation system is involved in many other biological and physiological phenomena, including medicine and healing [14,82,140,141]. Accordingly, we find common pathways, analogous brain structures and regions repeatedly activated in pleasure-related rewarding activities. The significance of dopamine, morphine and NO in emotional processes is growing and we can now add compassion to this list of limbic associated generated behaviors.

Activations in lateral frontal or prefrontal cortices, as demonstrated for love [70], can also be indicative of more generally positive mental states, i.e., positive affect, as seen in relaxation techniques, listening to music, or meditation

[11,14,28,65,142]. Clearly, further research is necessary. In addition, brain activity can exhibit highly fluctuating patterns, i.e., unstable or dynamic, with reference to varying psychological, physiological, and environmental factors. Nonetheless, CNS commonalities seem to exist and these especially concern (pre)frontal and limbic "shares" in the neurobiology of love and compassion.

Recent studies revealed a pathway for 'limbic touch' [70] that bypasses somatosensory cortices and directly activates parts of the insula, thereby evoking pleasant feelings related to touch and regulating emotional, hormonal, and affiliative responses to caress-like, skin-to-skin contact between individuals [143]. Limbic touch may thus be an analogue term to 'interoception', which is known to be related to anterior cingular (limbic) and insular signaling. The demonstrated CNS activity pattern involved in such phenomena overlaps with what has been described for maternal and romantic love and may thus reflect the sensory-emotive component that is common to and crucial for caring relationships, including compassion [70,144]. However, romantic and maternal love are not all the same: Besides data indicating specific as well as overlapping CNS activity (the latter represents the primary focus of this work), results obtained for romantic love were generally more significant in an attempt to examine these different conditions by modern neuroimaging means [70]. Friendship and love share common CNS features, even in physiology. However, they are not identical: Friendship, in general, seems not to be coupled to love, that is, friendship shows distinct neural and neuroanatomic activity patterns – and vice versa [70]. However, this assumption is due to specific patterns emerging in both states. The neurobiological motivation-reward axis, though, which is a common and general feature, i.e., non-specific, is certainly involved in both phenomena. In compassion we see the same separation of degree of emotion "supplied". Clearly here a link of sympathy encompasses some form of link but the degree may not be so strong as found in love. Also, feeling with someone, i.e., being compassionate or empathic, may also involve an activation of the mirror neuron systems (Figure 1). Friendship, sympathy or even love, or 'touch', are not mandatory for this reaction or state.

Love activates specific regions in the reward system, as described above, and this includes a suppression of activities in neural pathways associated with the critical social assessment of other people and with negative emotions [70]. In particular, love – and other states that involve robust reward signaling – reduces the ability to critically judge [70], i.e., impaired emotional judgment [145], decreases fear [70], and lessens the assessment of social trustworthiness [146]. Additionally, love-pleasure-related activation/deactivation patterns of lateral prefrontal cortices lead to reduced depression and enhanced mood, i.e., 'happiness', particularly in the left hemisphere, when activated (lateralization or asymmetry with left-anterior enhancement) [142,147]. Clearly, once one has become closely familiar with a person, the need to assess the social validity of that person is reduced [70]. These findings therefore may help to explain why 'love makes blind' [70], and in parallel, endorphin- and endogenous morphine-associated memory effects could play a role. In fact, the neural mechanisms suppressed here might be the same that, when active, are responsible for maintaining an emotional barrier towards less familiar people, corresponding to the avoidance behavior observed both in rats and voles against pups or potential partners, which is reversed by administration of oxytocin [102,103]. Taken together, a push-pull mechanism has been suggested for attachment: Attachment on one hand deactivates areas mediating negative emotions, avoidance behavior, and critical social assessment, and on the other, it triggers mechanisms involved in pleasure, reward, and appetitive motivation [11,70].

Pleasure and reward can activate behavioral patterns, or they may even break-up behavioral 'torpidity': Curiosity drives our motivation and actual behaviors towards new goals and 'fresh encounters', stimulating a search for 'new ways' and solutions, or partners, thereby involving spontaneity, appetence, and appetitive motivation [11,14]. Biologically beneficial and/or pleasurable events that occur on our way, driven by curiosity, involve reward signaling, as described, yet again encouraging and amplifying these new behaviors. Rewarding behaviors henceforth get memorized for the goal of repetition and faster/better recognition later on (i.e., behavioral-cognitive short cut, learning), particularly involving hippocampal mechanisms [11,33]. However, negative events and experiences may cause the opposite neurophysiology to evolve, even including a physiological deactivation of behaviors and motivation patterns (i.e., aversive motivation, apathy), or memory deterioration [33,148]. Hence, stress is a common trigger or cause of negative events, such as diseases, and it has a major yet principally preventable, i.e., reducible, impact upon our life styles [32,33,140,149–152]. Since love, compassion and pleasure may enhance positive or healthy behaviors and beneficial motivations by their rewarding capacities, love can be – in fact: it is – a tool in stress reduction, as illustrated. Social support and bonding, as they appear in the face of stress and challenge, may thus help to promote healthy life style modifications, therefore involving 'positive physiology' and 'positive psychology', i.e., feelings of wellness or well-being, yet integrating stress response and other molecular pathways [11,14,42,43]. For example, oxytocinergic pathways that originate within the hypothalamus and project to the VTA are necessary for maternal behavior, as are mesolimbic dopaminergic projections coming from the VTA [11,102,153], again indicating a connection between attachment behaviors and pleasure pathways. Thus, the association between social bonding and reproduction, as seen, e.g., in mother-infant interactions, may have contributed, in an evolutionary sense, to the selection of neurochemical systems involved in the occurrence of stress reduction, autoregulation and attachment behaviors [3,32,33,37,149,154,155].

Love, Spirituality and the Neurobiological Paradigm – is that the Whole Story?

One may now wish to know how this all relates to spirituality, religiosity and whether there is 'more' behind the said phenomena than pure neurobiology. Since this is more or less a philosophical question that was not the primary focus of this work, we won't dwell extensively upon the various implications of the neurobiological paradigm and its borders. However, we find the model of the Triune Ethics Theory (TET) by Narvaez [157] quite helpful in that it extends our views beyond the 'box' that we have investigated

with our work until this point: TET examines the neurobiological roots of morality and motivational principles and concludes that both are interconnected and built by a bottom-up process – i.e., TET is a bottom-up theory which fits very well to our hypotheses. Accordingly, TET states that motivation is formed by unconscious emotions that predispose one to behave in certain ways. Furthermore, early motivational experiences influence the personality formation and behavioral and motivational patterns as expressions of the individual (i.e., trait), however, depending on the actual and specific situations the individuals encounter, specific and 'new' reactions are still possible (i.e., state). And finally, there, theoretically, exists a description of conditions for an 'optimal human moral development', which is neither state nor trait, but more or less 'human' or general by its nature, i.e., blueprint. This latter aspect clearly opens our views into the realm of moral or spiritual intelligence or a possible concept that is broader than the survival of the individual, secured by its own neurobiological autoregulation.

Also, happiness and contentment are terms than can be examined biologically or spiritually likewise. For example, chills or goose bumps have a deep evolutionary root since they indicate the need for protection and warmth, particularly in the mother-child relationship [158]. Chills, however, come together with arousal and 'peak moments' that, for example, seem to involve dopamine and particularly oxytocin signaling pathways. In any way, the brain's reward physiology is of significance here and indicative of neurobiological and emotional peak states [156,158]. Yet, the very same peak experiences that appear to occur when people go through higher spiritual or religious 'mastery moments', i.e., 'enlightenment', may still have an overlap with brain physiology and functioning [11,159]. These states seem to correspond to 'global binding' experiences or 'unification states' that are definitely spiritual by their nature or by their individual content and that people could experience and frequently report during deep meditation, particularly with a higher level of experience and performance [159]. However, these reports resemble very much the descriptions of people in more 'worldly' or biological environments. Interestingly, these reports also include a high level of 'compassion' or 'love' for the world and other beings and may still have a neurobiological and measurable (i.e., 'objective') cause or effect, e.g., a high-amplitude gamma synchrony in the electroencephalogram of deep meditators [159].

The question is: Is spirituality a biological phenomenon that simply enables the individual to cope with stress and the species to survive and adapt through 'hard times'? This could very well be the case. However, the said relationship could also be the other way round, since the presumably 'objective' or third-person effects and measurements depicted in this work could correspond – or not correspond – to the 'subjective' first-person perspective (and also to the cognitive or the emotional perspective (Figure 1), which may or may not correspond to each other), and we do not know, in either case, which was there first, i.e., which was the cause and which the effect. And even more, there is some possibility that these events occur simultaneously and have another 'cause' outside the overall scientific paradigm (i.e., the 'zero-person perspective'): Clearly, science has only started to dive into this realm and a truly transdisciplinary approach is the only way we see that could give answers – if any – to some of the questions raised, including the basic assumption that the various phenomena observed have some kind of connection at all and don't occur simultaneously only by accident.

Why does meditation decrease the perception of stress on one hand and the basolateral grey matter density in the amygdala on the other of otherwise healthy meditators (and this only after eight weeks of meditation training) [160]? Why are similar observations and brain structures (to be involved) found in learning and ontogenesis and in infant development – and why do these processes involve common neurobiological signaling systems [14,42,43,82,156,161]? Why can the administration of dopamine (i.e., the experimental enhancement of endogenous dopamine levels) to otherwise spiritually or, in terms of religiosity, 'sceptical' people make them become 'believers' – or why there seems to exist a neural foundation of religious belief, as well as a clear biological connection between neural markers and religious convictions, even towards political attitudes, religiosity and stress vulnerability (or resilience) [162–166]? To be honest, the natural sciences – including neurobiology – have, to our knowledge, no sufficient explanatory answers as to all of these questions and their derivations or whether the answer possibly lies beyond their paradigms. However, it may not be the goal and the duty of the neurosciences to search such answers outside their own realm and borders, since this would not be 'scientific' in a more general sense. And maybe this reveals a core problem of understanding – and misunderstanding – when it comes to such transdisciplinary questions of great relevance for understanding of the nature of the human mind, the body and mankind as a whole.

Conclusions

Love phenomena act via common neurophysiological pathways. More precisely: Besides specific effects that are part of the neurobiological concept underlying love, numerous non-specific constituents and overlapping interrelations of love-pleasure mechanisms exist. These latter capacities that are imbedded in the love concept thus point towards common signaling pathways: We surmise that the shared signaling found in love and related experiences, i.e., compassion, is closely associated with CNS limbic reward and motivation activities, which are connected to pleasure phenomena and the well-being experience that is part of love, attachment and social bonding, as well as settings that more generally involve high levels of social support and closeness, i.e., 'connectedness'. Within these experiences also exists a domain for the emergence of 'spirituality' and its occurrence in religious settings and encounters.

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