The Neurobiology of Love

Tobias Esch[1, 2] & George B. Stefano[2]

[1,2] Charité - University Medicine Berlin, Institute for General Practice and Family Medicine, Schumannstrasse 20/21, 10117 Berlin, Germany.
[2] Neuroscience Research Institute, State University of New York, College at Old Westbury, Old Westbury, NY 11568, USA.

Correspondence to: Dr. G.B. Stefano,
Neuroscience Research Institute, State University of New York,
College at Old Westbury, Old Westbury, NY 11568-0210, USA.
FAX: 516-876-2727, PHONE: 516-876-2732,
EMAIL: gstefano@sunynri.org

Submitted: June 21, 2005 *Accepted: June 23, 2005*

Key words: **love; stress; limbic system; reward; pleasure; endogenous morphine; dopamine; attachment; sex**

Neuroendocrinol Lett 2005; **26**(3):175–192 **PMID:** 15990719 NEL260305R01 © Neuroendocrinology Letters **www.nel.edu**

Abstract

Love is a complex neurobiological phenomenon, relying on trust, belief, pleasure and reward activities within the brain, i.e., limbic processes. These processes critically involve oxytocin, vasopressin, dopamine, and serotonergic signaling. Moreover, endorphin and endogenous morphinergic mechanisms, coupled to nitric oxide autoregulatory pathways, play a role. Naturally rewarding or pleasurable activities are necessary for survival and appetitive motivation, usually governing beneficial biological behaviors like eating, sex, and reproduction. Yet, a broad basis of common signaling and beneficial neurobiological features exists with connection to the love concept, thereby combining physiological aspects related to maternal, romantic or sexual love and attachment with other healthy activities or neurobiological states. Medical practice can make use of this concept, i.e., mind/body or integrative medicine. Thus, love, pleasure, and lust have a stress-reducing and health-promoting potential, since they carry the ability to heal or facilitate beneficial motivation and behavior. In addition, love and pleasure ensure the survival of individuals and their species. After all, love is a joyful and useful activity that encompasses wellness and feelings of well-being.

REVIEW ARTICLE

INTRODUCTION

What an interesting phenomenon love is! Almost everybody can relate to a state of "being or falling in love" even though it is difficult to define love. In addition, depending on the background or "current state" we get a vast number of variant answers to our questions about love.

Following common knowledge, love is a strong, passionate affection for a person [31]. Hence, the Oxford English Dictionary defines love 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 [31]. However, only recently has the biology of love, and in particular its neurobiological aspects, become a focus of basic science. Medical, or health, implications related to the love physiology are still speculative, i.e., mainly not proven. Although at first it may sound logical that love – given its biological function to ensure the survival of a species via social attachment, gathering, copulation and reproduction – is a phylogenetically healthy activity, 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 [26,31].

In this report, evidence for common neurobiological pathways underlying the love phenomenon will be found. Love's neurobiological mechanisms will also be discussed in the light of medicine and health.

What is love?

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 [26,77,193]. In science, however, love appears to be a hypothetical and multi-dimensional construct with many interpretations and implications [26]. Love and its various emotional states and behaviors are rarely investigated by scientific means. In part, this may be due to the fact that love has always been the domain of poets and artists, maybe psychologists and clinicians, but has certainly not been considered to be right within the scope of common experimental science, i.e., neurobiology research [26]. Emotions and feelings such as attachment, couple and parental bonding, and even love – presumably typical of higher mammals and neglected for centuries by the experimental sciences – have now come into the focus of neuroscientific research in order to elucidate their biological mechanisms and pathways [118]. 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 involves having an emotional bond to someone for whom one yearns, as well as having sensory stimulation that one desires [105]. The word "love," however, derives etymologically from words meaning "desire," "yearning" and "satisfaction" and shares a common root with "libido" [105,137,168]. 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 [105]. Love therefore possesses a close connection not only with reward and pleasure phenomena, but also with appetitive and addictive behaviors [57].

Naturally rewarding activities like love boost a flood of stimulating signaling molecules [54,57,191]. 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 [57]. The distinction between natural and artificial rewards can also be made by the build-up of appetence. Natural rewards, i.e., pleasurable experiences like eating or sex, usually depend on a preceding build-up of appetence (e.g., sexual desire) to fully develop their pleasure potential [78,172,173]. Following the pleasurable experience, appetence decreases and then needs a certain time span to reach its former levels and intensity. During this time, the same "appetizing" experience can even induce aversion [173]. Addictive drugs, in contrast, immediately build up high appetence levels that are not released completely or only for a short time after consumption [130,131,153]. This frustrating fact produces even more appetence: One can not stop the pleasure-seeking activity that now starts to control normal behaviors (i.e., motivational toxicity) [57]. 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 [17,200]. Thus, love and addiction are evolutionarily and behaviorally interconnected, but they are not same, at least not in relation to artificial drug ingestion. Being "addicted to love," however, refers to this interconnection.

The key element for achieving beneficial effects is 'balance', i.e., aiming at a state of dynamic balance/rebalance, that is, having biological feedback and control systems in place that keep natural autoregulatory pathways within a certain, healthy range [54,57]. Thus, love can be viewed as a dynamic process that represents the result of different components probably subserved by distinct neural substrates at different times [118]. As such, some steps can be identified, e.g., its beginning ("falling in love"), which is the process of attraction, followed by the attachment process that, in some cases, can last forever [118].

Selective social attachments and the propensity to develop social bonds are necessary features of the love concept [26]. Furthermore, this concept is associated with parental as well as sexual behaviors [26]. Both types of attachment and love, i.e., sexual or romantic versus parental or maternal, can provide a sense of safety and reduce anxiety or stress – important for a healthy life and, e.g., balanced way of decision making [26,57]. Biologically, to "fall in love" is the first step in pair formation [117], involving attachment and bonding as well as romantic, sexual, and parental behaviors and experiences, e.g., lust, pleasure, joy and happiness [57]. Clearly, love has a positive connotation. However, it seems to be a rather complex phenomenon and not only implicates sensational elements or behaviors, i.e., sensation- and approval-seeking, but also psychological, emotional and neurobiological portions. In the end, it all has to serve biological goals: Its function exceeds that of reproduction alone, since love also facilitates the establishment of long-lasting relationships that are related to trust and belief and may ensure support or protection under challenging circumstances [48,51,117,171]. Thus, love – and the act of falling in love, in particular – represents a physiological and transient state that is related to specific, i.e., biologically useful, behaviors, possibly involving beneficial behavioral changes and social interactions [117].

The most accepted form of an enduring social bond, within the love concept, is maternal attachment [26]. The idea of motherly love [76] implies a selective behavioral response by the parent to its offspring, i.e., parental love [26]. Hence, the tender intimacy and selflessness of a mother's love for her infant occupies a unique and exalted position in human conduct [10]. It provides one

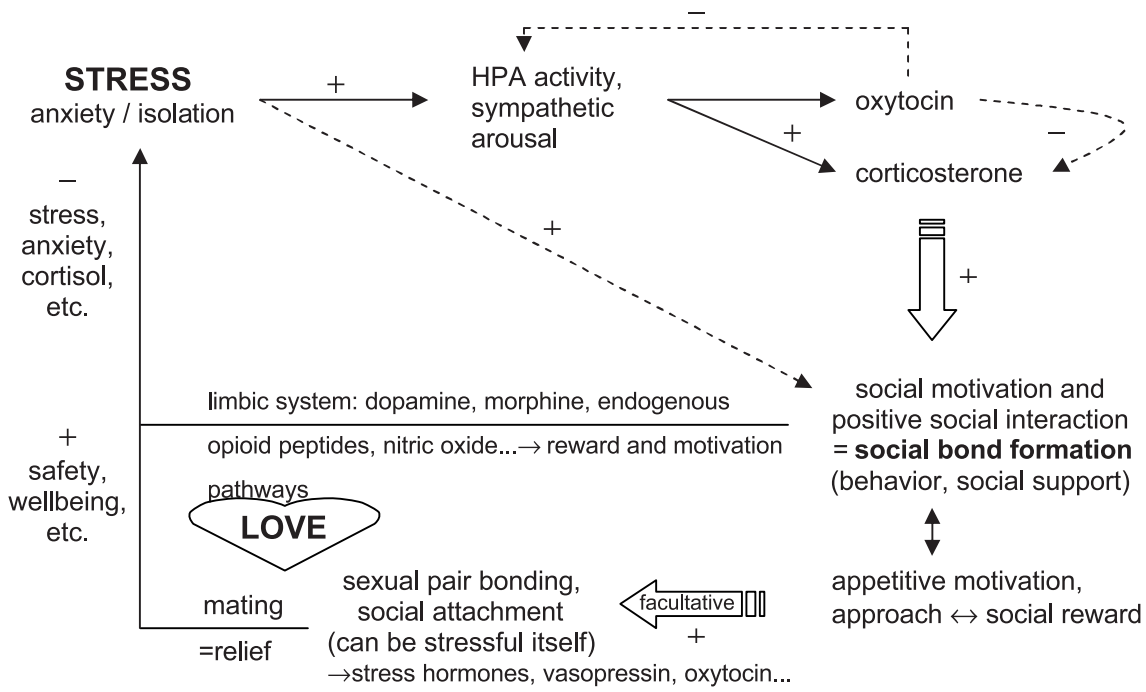

Figure 1. *Stress and its relation to social bond formation and love.*
References see text. HPA – hypothalamic-pituitary-adrenal (axis).

of the most powerful motivations for human actions and behaviors [10]. Sexual behavior, on the other hand, is closely related to attachment as well, but they are not synonymous [26]. Sexual activity can occur in the absence of social attachment, and many forms of attachment exist that do not involve sexual behaviors [26]. However, in humans, the most desired sexual partner is often – and simultaneously – the object of strong feelings of attachment [26].

In monogamous mammals, pair bonds provide a social matrix for sexual behavior [26]. Mating promotes social preferences [26,207], possibly because oxytocin and/or vasopressin are released during sexual interactions. We see that sexual, romantic, or parental love and attachment overlap: Maternal and romantic love share a common and crucial evolutionary purpose, namely the maintenance and perpetuation of the species [10]. Both ensure the formation of firm bonds between individuals by making this behavior a rewarding experience. It is possible that they share a similar evolutionary origin, and it is likely that they also share some common neurobiology [10].

Behavioral theories and models of attachment and love have focused on either caregiver-infant interactions or adult pair bonding [26]. Obviously, similarities exist between the behaviors associated with parent-infant and adult romantic attachments. In fact, several investigators have suggested that these types of love share common biological substrates [26,62,140]. We, therefore, focus on the neurobiological commonalities between parental and romantic love in the following, however, not excluding remarks on interesting and important differences, when indicated.

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 [11,46,50,183,208]. Hence, love or lust, and the joy that is imbedded in the love concept, seem to be not only individually rewarding but also behaviorally and biologically advantageous experiences, thereby protecting the species [46,57,146]. Questions like these have recently become a focus of evolutionary psychology, a field of sociobiology [46], 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 [57,169]. It is surmised that some degree of strong, yet manageable, stress may be necessary for very strong bonds to form [169]. However, if socializing "in the face of stress" does not occur, diseases may be introduced [26,55,58,59,60]. 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 [26,58,60]. 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 [60,152]. This correlation between chronic or massive stress could finally inhibit the new forming of bonds and attachments, leading to social and physiological deprivation, or regulatory imbalances and inflexibility, thereby compromising healthy (auto)regulation [26,51,52]. However, within a homeostatic range, stress-related physiological processes, including hormones of the HPA axis, can promote the development of social bonding [43]. In addition, positive social interactions may help to create physiological states that are anxiolytic and stress reducing, i.e., health promoting [26,48, 52,54]. Thus, balance is a key concept in social bonding and love, including related neurobiology (see below).

While acute stress obviously induces subsequent reproductive behaviors and social contact, chronic stress may lead to a strong reduction in the abilities to propagate [46]. Furthermore, with an increasing population density, as shown for example in rodents and primates, social stress and aggression rise, accompanied by enhanced infertility rates, susceptibility to infections, blood pressure, atherosclerosis, neural, cardiovascular, and renal damage or diseases [48,51,55,56,58,59, 60,162]. It is important for biological organisms to possess programs and strategies that buffer against stress and social isolation [46]. Hence, love can be such a mechanism [46]. On the other hand, higher animals bear a mechanism within themselves that negatively selects individuals with unsuitable behavioral abilities, leading to infertility or, ultimately, death [85]. Thus, stress and love are biologically interconnected: Individuals that possess better or more effective strategies to cope with stress also show better immune functions and sexual performance, and thus have a direct benefit for survival and reproduction, i.e., they possess an advantage for passing on not only their genes in general, but also their coping methods [46,55]. Reproduction therefore not only relies on technical abilities to love and copulate but much more on psychological means to "do the right thing," i.e., overcome stressful situations and cope with challenges, and even the ability to relax [46,52,182]. Hence, evolution positively selected for biological mechanisms that help to cope with stress, that is, facilitate stress reduction and adaptive behaviors – experiences like pleasure, lust and love [54,57]. Taken together, happiness, pleasure and well-being, as well as touch, social contact and support, are related to the love concept and, via stress reduction and protection, represent a distinct and important evolutionary factor [46,76,100]. This may be the reason why higher biological organisms tend to be pleasure-seekers [46,57,76,100]. After all, these psychological phenomena have a biological match, and it is imbedded in central nervous system (CNS) structures and pathways, e.g., neurobiological reward and pleasure pathways [54,57]. Interestingly, the physiological processes are, in part, present in simpler organisms devoid of cognition [180].

Feelings of security and support lead to the facilitation of trust and belief (see below), including "meaning and spirituality," thereby inducing positive motivation and behavior [57,170,171]. We will focus upon the specific neurobiological pathways and signaling molecules that are involved later on, showing that lust, pleasure and love have physiological correlates, i.e., CNS reward and motivation circuitries [14,46,57,136]. In species that form heterosexual pairs, rewarding sexual activities are associated with the formation of social attachments and bonds [28]. Sexual behavior, however, can also be physiologically stressful for both sexes [26], 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') [25,54,57,121,145,159,186,217], 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 [159]. These are some of the same events that occur when one is exposed to sexually charged stimuli, or engaged in sexual act [112,113,163,205]. These cardiovascular events are initiated at the level of cingulated, amygdalar, and hypothalamic CNS processes, as well as their projections into higher level cerebral cortex, further altering heart rate under stressful or sexually aroused conditions [82]. 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 [83]. These include changes in cardiac autonomic tone, with a shift from the cardioprotective effects of parasympathetic predominance to massive cardiac sympathetic activation [84]. 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 [159,186].

Furthermore, oxytocin, a major player in love physiology, has also been associated with stress reduction [26]. In humans [27,30,197,198], oxytocin inhibits sympathoadrenal and stress response activity, including the release of adrenal corticoids (Figure 1). The effects of oxytocin on pair bonding or other forms of social attachment may therefore be related to the autonomic, i.e., autoregulatory, role of oxytocin in stress reduction [26]. Steroid exposures, as seen, for example, during highly stressful experiences, have the capacity to produce both structural and behavioral changes [55,58,60,70], including changes that may alter the propensity for social behavior [26]. Here, early development seems to be of particular interest: Prenatal and perinatal stress or treatments with stress hormones, as

well as ontogenetic experiences like varying amounts of parent-young interaction, can affect adult patterns of social and sexual behaviors later in life [26,158,203]. Glucocorticoid levels are high in late pregnancy and may decline at delivery [26]. Hence, progesterone and the glucocorticoids have comparable chemical structures and share many physiological and behavioral properties and may, therefore, occasionally exert similar effects on peptide binding [143]: These steroids could act separately, or in concert, to influence social behavior [26]. Thus, social preferences, upon which attachments are formed, may be developmentally altered by stress and/or steroid hormones, i.e., HPA axis activity, especially when administered or encountered in early phases of life [26]. Moreover, treatment with vasopressin, another key player (see below), during the first week of life in rats has shown to reduce gene expression for the oxytocin receptor in the paraventricular nucleus (PVN) during adulthood [138,199]. Since vasopressin is integrated in the HPA axis and sensitive to androgens, i.e., steroids, it has been speculated that developmental changes associated with perinatal stress or gender-dependent androgenization could alter the subsequent sensitivity of the oxytocinergic system [26]. Furthermore, male prairie voles, and to a much lesser extent females, that were exposed to vasopressin injections during the first week of their life were, as adults, more aggressive towards intruders than were untreated animals [26]. Thus, hormones involved in the love physiology, such as vasopressin, demonstrate a relationship between early development, stress, physiological "love signaling," and subsequent social or protective behaviors.

Subjects in love show higher cortisol levels as compared with those not experiencing this state [117]. 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 [117]. This physiological state of alertness, associated with love, may help to overcome neophobia, although this is still a speculative aspect [117]. 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 [26,42,43,79,109, 117,123]. Thus, love seems to be a complex phenomenon and, with regard to stress, an ambiguous experience, i.e., double-edged sword: Love itself can be stressful, but it potentially serves to lower stress levels over the long term. Furthermore, an association between HPA axis activation, following stressful experiences, and the development of social attachment becomes obvious, which, in turn, promotes physiological states that reduce anxiety and related negative sensations [81, 108,125,169]. Interestingly, given elevated cortisol as a non-specific marker of early love states, no differences in cortisol levels between women and men in love were observed over the long term [117]. But here, we have to consider that cortisol levels are difficult to measure, since they show sensible and variant patterns that differ over day and night and between individuals experiencing different levels of stress. Additionally, cortisol depends on emotional states in a much broader sense: Emotional lability is associated with a more labile regulation of cortisol and testosterone secretion, meaning that an observable intraindividual variability of basal stress hormone secretion may contribute to the vast interindividual variability noticed in psychoneuroendocrine stress research [4]. Hence, statements on cortisol levels with regard to stress, love, and gender differences have to be drawn carefully.

Evidence for attachment formation comes from behavioral changes associated with mammalian birth, lactation, and sexual interactions [26]. Mammalian birth is clearly a stressful experience. In the mother, physiological events preceding and accompanying parturition involve exceptionally high levels of adrenal activity and the release of various peptides, including endogenous opioid peptides, oxytocin, and vasopressin [99,107]. As mentioned before, stressful experiences or challenges may encourage increased social behaviors and attachment [26]. Hence, comparatively high levels of HPA axis activity or other indicators of stress or sympathetic arousal, and a subsequent release of oxytocin, have been measured under conditions that commonly precede or are associated with the formation of social bonds [26]. These bonds, as illustrated, may than buffer against stress, facilitating social support, security, and closeness, since the presence of a partner may provide a social form of stress relief [26,52,79]. Taken together, positive social behaviors, including social bonds, may reduce HPA axis activity and stress, and central neuropeptides, including vasopressin and oxytocin, have been implicated both in social bonding and the central control of the HPA axis [26]. Threatening or challenging situations may therefore encourage the return to a secure base or otherwise strengthen social bonds [139]. Oxytocin, however, is capable of inducing positive social behaviors and both, oxytocin and social interactions, decrease activity in the HPA axis, i.e., stress [26,41,48,52,55,58,60,198]. Social interactions and attachments then activate endocrine or autoregulatory signaling systems that are able to further reduce stress, i.e., HPA (hyper)reactivity, yet modulating emotions and the related autonomic nervous system's involvement, thereby, perhaps, accounting for health benefits that are attributed to loving relationships (Figure 1).

Motivation and behavior

Motivation concerns aspects of intention or activation [57]. Consequently, it lies at the core of biological, cognitive and social regulation [157]. Motivation is highly valued in health care since it produces behavioral changes or adjustments and can mobilize others to act [157]. A large amount of behavior can be explained by simple processes of approaching pleasant and avoiding painful stimuli, i.e., motivational behaviors [177]. Hence, motivation may be divided into two categories

– appetitive and aversive motivation [57]. Appetitive motivation concerns behaviors directed towards goals that are normally associated with positive or hedonic, i.e., pleasurable, processes (food, recreational drugs, sex etc.) [57]. In contrast, aversive motivation involves getting away from hedonically unpleasant conditions [17]. Consequently, two fundamental forces rule motivation and subsequent behavior: Pleasure and pain [57]. It has been suggested that pleasure may be associated with *beneception*, events that facilitate survival and, thus, benefit the organism or species from an evolutionary perspective [196]. Pain, on the other hand, is associated with *nociception* [57]. The latter describes conditions that may have undesirable biological consequences for an organism [17,196]. However, pain and pleasure potentially merge into one another [57]. With regard to specialized brain compartments involved in motivational processes, the physiological substrate for appetitive or aversive motivation primarily lies within the limbic system [34,50,60,86,186] (see below).

Reward and punishment are functionally and anatomically interconnected [57]. 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 [57]. 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 [130,131]. The essential neurotransmitter of this connection is dopamine. Clearly, the VTA or mesolimbic dopamine system represents a rather old, but very effective, part of motivational physiology and behavior [57]. 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 [132]. 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 [130,131]. The hippocampus participates in recording memories of an experience, including where, when, and with whom it occurred [132]. The frontal cortex, however, coordinates and processes all information and consequently determines the ultimate behavior [57]. 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 [132]. The more rewarding an activity is deemed, the more likely the individual is to remember and repeat it [132].

The tendency to approach or avoid particular social stimuli or biological objects is fundamental to attachment behaviors [26]. Some stimuli may be innately positive or elicit positive responses, while others, particularly those that are novel or produce a sense of insecurity, can be aversive or fear-inducing, even eliciting stress responses [26,55,58,60]. Specific physiological states may facilitate positive or beneficial social behaviors, including affiliation, attachment formation and reproduction. However, some states may encourage self-defensive or aggressive behaviors – states that may, but not in every single case, be incompatible or difficult to combine with love and attachment [149]. Peptidergic autoregulation systems, involving oxytocin, may serve to inhibit defensive behaviors associated with stress, anxiety and fear (Figure 1). In addition, they may allow positive social interactions to develop [26]. However, these same peptidergic systems, including reward pathways that elicit pleasurable feelings and appetitive motivation, can be related, in some cases, to arousal, stress or even stress reduction: The positive and even health-promoting aspect of appetitive motivation, and its possible association with stress reduction, love and attachment, may, as a "side-product," facilitate a pleasure-love search, that is, a desire to socialize that may also introduce addictive behaviors (as discussed above).

Steroid hormones, related to stress physiology and the reproduction cycle, can influence oxytocin receptor binding in the CNS, particularly in the olfactory-limbic-hypothalamic axis, which has been implicated in social and sexual behaviors [93]. For example, progesterone and/or glucocorticoids are capable of inhibiting functions of oxytocin or its receptor within the CNS, while possibly increasing oxytocin receptor binding in other parts, i.e., limbic [71]. Hence, site-specific modulation of peptide binding by specific steroid hormones could account for at least some of the regulator effects of steroids, or stress, on maternal or sexual motivation and behavior [26].

Trust and belief

Trust and belief often have a negative connotation in science[170,171,186]. For example, the placebo effect seen in medicine is frequently said to be fraudulent since it obviously relies on trust of a patient or his/her belief in a certain doctor or therapy [54,57,170,171,186]. Effects like these, that are subjective by nature, are from an "objective science perspective," regularly held to be illusory or unscientific [54]. However, trust and belief undoubtedly play a major role in health, science, and medicine [48,57,170,171,186]. It has been suggested that the placebo effect is basically mediated by dopaminergic – and possibly morphinergic – reward mechanisms and that this placebo-related reward physiology is associated with positive therapy expectations, i.e., expected clinical benefits [36,54,57,186]. Hence, placebo effects may involve anticipatory pleasure and positive motivation [57]. The placebo response, as described, relies on trust and belief, and this connection has its neurobiological roots predominantly in limbic or frontal/prefrontal brain activity [36,37,119,167].

The brain's reward and motivation circuits, responsible for the placebo physiology, include different CNS regions that may serve various separate functions, but overlap in their reward signaling pathways (see below). Almost all of these structures and mechanisms exhibit some form of association with cognitive functions, trust or belief [54,69,186]. Hence, belief has an emotional

component in that the brain's motivation and reward circuitry, linked to memory processes, will be reinforced with a positive emotional valence attached to the person, idea, or thing that is believed [54,170,186]. This emotionalized memory, potentially accompanied by "somatic markers" (e.g., pleasant bodily sensations that may escort an emotion), sets the "feeling tone," i.e., it strongly influences what feels right to a person [57, 186]. Pleasure and emotion may reinforce a belief or trigger positive physiological reactions even against rationality [183,184]. Thus, belief in a doctor, therapy, sexual partner etc., as well as the belief in love, in general (i.e., religious beliefs), may stimulate naturally occurring health processes [54,57,65,170,185]. These subjective processes may predominantly be based on endogenous autoregulatory signaling molecules like endorphins and endocannabinoids, possibly originating in limbic pathways [54,182,186]. Moreover, belief affects mesocortical-mesolimbic appraisal of a pleasurable experience, leaving one, for example, well and relaxed [57]. Taken together, the subjective modulation of incoming information in the brain – e.g., following prior stimulation of the sensory organs – may be an important factor in love, pleasure, and placebo phenomena. This may be particularly true when positive qualities or experiences like pleasant sensations, touch, attention, and feelings of protection, in general, are involved [54,57,65,185].

Limbic functions: Reward and pleasure

The biological mechanism mediating behavior motivated by events commonly associated with pleasure is called 'reward' [57]. It is usually governing normal behavior through pleasurable experiences [17]. Pleasure, however, describes a 'state or feeling of happiness or satisfaction resulting from an experience that one enjoys' [1]. 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 [57]. Hence, an intimate association between reward and pleasure exists [17,132]. 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 [50, 54,57,58,60,154].

Love has the capacity to influence the autonomic-emotional integration system, i.e., limbic system [54, 160]. Here, the autonomic nervous system (ANS) and emotions are wired together. Furthermore, sympathetic activity and stress hormone production are imbedded in underlying autoregulatory circuits [50,52,60]. An association of love with emotions, neurotransmitter and stress hormone production (Figure 1), autonomic responses, behavior, and mood states becomes obvious [54]. 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 [49,54]. Hence, an 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, i.e., love [2,16,57,156,213].

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 [57]. 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 [130,131]. Reward pathways are evolutionarily ancient like limbic structures. In fact, these pathways are essentially of limbic origin [54,57]. For example, prefrontal or orbitofrontal cortices, cingulate gyrus, amygdala, hippocampus, and nucleus accumbens participate in the reward physiology [186]. 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 [10,63,97,155]. Memories of the pleasure of wellness, i.e., "remembered wellness," are accessible to this system through hippocampal mechanisms [54]. 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 [17,135]. An important neurotransmitter here is dopamine [57,212]. 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 [15, 17,57,132,135,212]. Thus, pleasure induction involves a circuitous reward pathway, first activating a descending MFB component and then, as described, the ascending mesolimbic dopamine pathway.

Pleasure and reward may not only serve entertainment or enjoyment, but may also govern behavior, sexual reproduction, and personal growth [57]. The striatum (caudate nucleus, putamen, globus pallidus), for example, contains cells that respond to food and drink reward [10], and it is activated by monetary reward stimuli [47,102,165] or psychomotor stimulants, e.g., cocaine [18], as well as sexual arousal [8,10,61,96,151]. Hence, a hypothalamic activation specific to romantic love could reflect the component of erotic arousal inherent to this sentiment [8,10,61,96]. Regions commonly activated in love, as known so far, are strongly involved in reward physiology, comparable to an acute administration of euphoria-inducing drugs, such as cocaine [10,18,164]. It has therefore been speculated that the particular subregions in the reward and motivation systems activated in love phenomena and physiology reveal a general, i.e., non-specific and modality-independent, network that is specialized to mediate attachment [10]. However, 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 [15,57,130,131]. Ventral tegmental activation, as described, involves dopamine signaling [57]. Other neurotransmitters (e.g., GABA, glutamate, serotonin, the stress hormones noradrenaline and cortisol, as well as acetylcholine, nitric oxide, endorphins/opioid peptides, and endocannabinoids) may also play a critical role in reward physiology [57,154,204]. In addition, endogenous morphine/opiate production may be of importance [54,57,64,65,159,183,217].

Feeding, maternal behavior, or sexual activity can each be facilitated by opiate activation of the reward system [75,128,195]. The origin of the VTA (i.e., ventral tegmental 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 [17,54]. Obviously, endogenous morphinergic signaling plays a significant role here [54,57]. This is especially true since endogenous morphine biosynthesis, found in humans, vertebrates, mammals, and invertebrates [54,148,159,217], involves elements of dopamine synthesis and its metabolism [53, 54,57,189,218], thereby linking two critical signaling systems[219]. Specifically, endogenous morphine production has been demonstrated in limbic tissues, e.g., hippocampus and amygdala [12,159,176,217]. Morphinergic signaling has further been found to release constitutive NO [38], thus linking endogenous morphine and NO to limbic reward and pleasure pathways [57]. Taken together, limbic areas are connected to the frontal/prefrontal cortex which integrates emotion, memory, belief, expectation, motivation and reward processing, i.e., affective and motivational responses [116,186]. Also, prefrontal mechanisms may trigger dopamine, NO, and opiate release in the midbrain [201]. After all, the VTA serves as a appetitive motivation system for diverse behaviors, including sex, since it controls both normal and pathological behaviors [15,16,17,54].

Mating, i.e., sexual intercourse or sexual stimulation, releases oxytocin [25]. Together with vasopressin, this peptide is a key neurobiological transmitter in love and pair bonding [39]. Moreover, vasopressin production, as it is directly inducible by sexual stimulation, may also be enhanced by testosterone release, as part of the sex physiology [26]. Since mating and love involve pleasurable experiences and, therefore, release dopamine and/or increase sympathetic activity (at least in the beginning: Figure 1), this act is a substantially rewarding experience, yet facilitating appetitive motivation and arousal, which may increase the level of sexual stimulation (positive feedback). All these physiological features of the sexual component of love, mentioned above, may finally enhance sexual stimulation, testosterone, oxytocin, and vasopressin release until relief is found [26]. Furthermore, vasopressin may account for a fluctuating postcopulatory aggression that has been demonstrated, for example, in male prairie voles [26], which indicates territorial behaviors. Thus, the physiological relief that follows copulation may show different patterns in males and females, i.e., behavioral and physiological gender differences [28]. Finally, the activated systems, including sympathetic nervous system and stress response pathways, calm down in both sexes, leading to an overall sense of well-being that involves pleasure and reward activity [54,57]. Interestingly, an experimental treatment with vasopressin has been shown to be closely associated with increased activity in the nucleus accumbens, thereby pointing, again, towards reward physiology involvement, which is important for both sexes [26,67,209].

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 [26]. Dopamine agonists, capable of inducing reward and pleasure, release oxytocin, and interactions between oxytocin and dopamine have been reported in rats [106,161]. Additionally, high levels of oxytocin receptor binding have been demonstrated in the nucleus accumbens of prairie voles [87], 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 [73,219]. Interactions between oxytocin and catecholamines may therefore provide a mechanism for rewarding or reinforcing pair bonding [26]. 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 [26,144]. Taken together, it seems plausible that pleasurable sensations produced by sexual activities would provide mechanisms that reinforce behavior, thereby promoting its repetition [159]. 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 [159]. 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 [57,159].

The neurophysiology of love

Falling in love, given the initial uncertainty, lets our cortisol levels rise [117]. Increased cortisol concentrations, however, together with lower follicle stimulating hormone (FSH) and others [117], indicate the stressful and arousing conditions associated with the initiation of social contact. Furthermore, oxytocin plays a crucial role in parturition and lactation, i.e., postpartum period in mammals, which is characterized by milk production [26]. A pulsatile release of oxytocin not only induces myoepithelial tissue contractions necessary for the act of giving birth but also contractions of cells in the breast that produce milk flow [26]. Indeed, oxytocin is a key player in sexual behavior, since it is involved from its start – the process of falling in love – to subsequent outcomes, i.e., offspring. Also, oxytocin ensures trust, loyalty, and devotion, which seems to be important for

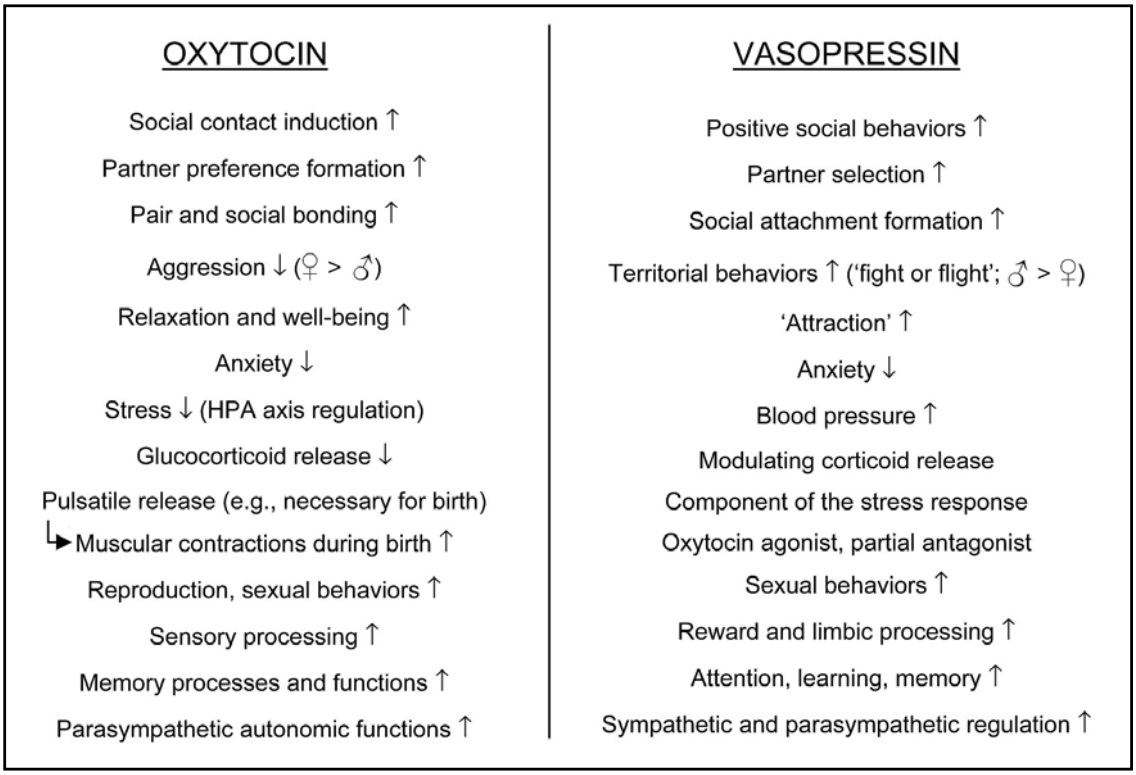

Figure 2. *Love physiology: Oxytocin and vasopressin effects*. Oxytocin and vasopressin are small peptides that have similar structures. They may have evolved from the same ancestral peptide [3] and thus are functionally and structurally interrelated. Both are involved in social attachment formation, prosocial and reproductive behaviors, including sexual and parental. They play a role in reward processes and may therefore be associated with endogenous opioid and opiate signaling, i.e., morphine, since this autoregulatory signaling system is crucial for attachment, pleasure induction, response to separation and stress reduction [54,57]. Further references see text.

intact or beneficial and lasting relationships [117,118]. Together with vasopressin, prolactin, and endogenous opioids, oxytocin reduces HPA axis (re)activity (Figures 1 and 2), and it further reinforces the attachment between mother and child, e.g., by changing olfactory characteristics and preferences to parents'/mother's odors [26]. Interestingly, milk contains high levels of oxytocin and prolactin, thereby additionally facilitating infant-mother attachment and bonding, as well as infant's nervous system development and the structural tuning of stress response mechanisms [26].

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 and desire [10,57,89,98,117]. In fact, most regions charted to contain vasopressin and oxytocin receptors in the human brain are activated by both maternal and romantic love [10,92,111]. 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 may have distinct binding sites and may be gender-specific [10,32].

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 [26]. However, the distributions of these receptors within the CNS vary across development and among mammalian species [9,88,93,110,142,166,202, 214]. 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 [26,138]. 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 [9], a fact that is further complicating analyses of pathways through which oxytocin and vasopressin affect social attachment behaviors [26]. In addition, catecholamines, endogenous opioids, and prolactin influence parental behavior as well, either by modulating the rewarding aspects of this behavior [140,141], pacing mother-infant interactions [19], or through their documented abilities to affect the release and actions of other peptides, including oxytocin [26,101]. Finally, release patterns of both neuropeptides vary since oxytocin appears to act faster and with more dramatic pulses, as compared to vasopressin [40].

Hormones generally act on the ANS to integrate attention, emotional states, motivation and social communication with behavioral, physiological, or environmental demands [55,58,60]. The ANS therefore

is essential for social attachment and love, and it also contains receptors for oxytocin and vasopressin [26]. Clearly, catecholamines, and other ANS signaling molecules, play a role in love phenomena, and love, on the other side, acts on autonomic functions and states, i.e., stress and stress reduction (see above). Falling or being in love makes us feel good and, at times, "out of this world." In fact, love produces states that resemble obsessive behaviors or disorders; while, in the case of love, thoughts much more than behaviors characterize the actual obsession, i.e., thinking about the object of love "all the time" [117,118]. Recently, researchers specified molecules inducing such mental states: Vasopressin and oxytocin, the stress hormones norepinephrine and cortisol, as well as "pleasure molecules" like dopamine, endocannabinoids and endorphins – possibly together with endogenous morphine – have already been mentioned and will be further investigated in the following text. In addition, blood drawn from individuals currently in love also revealed lower levels of serotonin, comparable to that of patients suffering compulsive-obsessive disorders [118]. This finding appears to be contradictory at first, since serotonin is known for its mood enhancing effects for which it is sometimes called a "pleasure hormone" as well. However, serotonin induces mental calmness, something that individuals who have just made an attractive social contact (i.e., first approach), yet started to fall in love and want to overcome neophobia, don't want to experience [117,118]. Thus, the early phase of love and attachment reminds us of a "roller-coaster," that is, hormones of the ANS and related neuropeptides are climbing-up and fall down again in a short period of time, thereby inducing different states that are necessary for a good relationship to begin and, later on, stabilize.

Another important hormone showing changes under love, and a somewhat surprising pattern of release, is testosterone since its concentrations vary in opposite directions in the two sexes: Men in love demonstrate decreasing testosterone levels, whereas women in the same condition produce more testosterone [117]. It has been suggested that falling in love may therefore include the tendency to temporarily eliminate some of the biological differences between the sexes, or to soften some male features in men and, in parallel, to increase them in women, including a more "outgoing" or aggressive behavior style [117,220]. However, this speculative aspect has to be thoroughly examined further before specific conclusions should be drawn.

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 [66]. However, the specific pathways involved as well as the significance of related estrogen signaling still are 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 [66]. Moreover, testosterone further enhances vasopressin levels in the medial amygdala, lateral hypothalamus, and the preoptical medial area, involved in aggressive behaviors [66]. 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 [26]. 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., feedback [26]. 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 in mood, affect, and motivation regulation [15,17,36,57]. 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 [17,216]. Accordingly, dopamine, interpreted here as a crucial 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 [57]. It is important to note that, based on new knowledge, there is a potential for endogenous morphine signaling to be part of this process [64, 65,73,175,185,219].

Enkephalin inhibits the release of oxytocin and vasopressin in the posterior pituitary gland, i.e., neurohypophysis (as opposed to the anterior adenohypophysis where the stress-related HPA axis is going through), and by doing so, opioid peptides may decrease vasopressin- (and oxytocin-) related memory and learning stimulation as well as oxytocin-associated breeding behaviors [20,126]. However, opioid peptides are a substantial and innate part of the love and reward/pleasure physiology, as are presumably the endogenous opiates, e.g., morphine [54,57]. In fact, recent information suggests that morphinergic signaling should also be part of the love-pleasure-reward hypothesis described earlier [64,65,73,175,185,219].

Endogenous morphine, both biochemically and immunocytochemically, has been found in various neural tissues, including within the limbic structures [12,13, 24,44,45,68,74,103,104,187,218]. 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 [20,117,118]. Additionally, reports demonstrate the presence of morphine precursors in various mammalian tissues, including brain [54]. Furthermore, an opiate receptor subtype, designated mu3, has been cloned, which is opiate alkaloid selective and opioid peptide insensitive [21], strongly supporting the hypothesis of an endogenous morphinergic signaling system [54,57, 148,159,217]. The psychiatric implications of this system have been examined, including brain reward circuitry [64]. Morphine, given its reported effects and those exerted via constitutive NO release [57,159,217], may thus form the foundation of a common signaling among love and pleasure phenomena, including attachment behaviors [10,54,57,127].

In general, morphine exerts immune, vascular, and neural down regulating activities, and endogenous opiate compounds are involved, as described, in the pleasure-reward system [57,181,189,190]. Indeed, morphine may allow one to make rational short cuts since being rationale, or dwelling upon single aspects in/of love, may sometimes not be appropriate, that is, too time-consuming or biologically dangerous [54,183]. In addition, mu receptors are critical to lust and reward and they may trigger feelings of wellness, which are essential for positive motivation, lasting relationships, and attachment [57,129]. These same pleasurable feelings are further involved in other biologically critical procedures, e.g., food intake [129], again demonstrating the core role of the love-pleasure-reward system in the survival of an organism and its species (see below). Interestingly, mice lacking mu receptors have been shown to be more susceptible to noxious stimuli – that is, they experience more pain – and, in contrast, to become less prone to addiction and addictive behaviors [129]. Moreover, stress perception and attachment formation are related to mu opioid receptor signaling: This opioid receptor system of the brain, for example, serves to associate the warmth and odor of a mother with her infant's feelings or memories of relaxation and wellness, i.e., remembered wellness, thereby essentially supporting infant-mother bonding [57,129]. Separation cries of infants upon separation from their mothers – causing high levels of stress, i.e., increased corticosterone concentrations – can be diminished by experimental stimulation of mu receptors, as well as oxytocin or prolactin injections [80,140,210]. Also, opiate signaling seems to modulate memory in a way that negative memories are erased, possibly enhancing more positive recollections or feelings of wellness [10,72]. Taken together, endogenous opioid/opiate binding mediates natural rewards and has been proposed to be the basis of infant attachment behaviors [129]. Furthermore, diseases characterized by deficits in attachment performance or behavior, such as autism, may be related to a malfunction in this signaling system [129].

DISCUSSION

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 [53,54,178, 182]. Accordingly, we find common pathways, analogous brain structures and regions repeatedly activated in pleasure-related rewarding activities.

Activations in lateral frontal or prefrontal cortices, as demonstrated for love [10], can also be indicative of more generally positive mental states, i.e., positive affect, as seen in relaxation techniques, listening to music, or meditation [35,49,50,54,57]. When teenagers listen to music of their choice, parts of the frontal (and temporal) lobe in the left hemisphere get activated [6,7]. In contrast, when they listen to music they dislike, analogous areas on the other side are active [54]. Pleasurable music, however, also stimulates deeper structures, i.e., limbic, again showing a left-right asymmetry with the more negative perceptions following activations in right hemispheric structures, e.g., parahippocampus and amygdala, related to anxiety or fear [6,7,54,160]. Furthermore, meditation has been shown to increase left-sided anterior activation of the brain, as measurable by various EEG techniques [35,54]. Davidson et al. recently suggested that this particular brain activity pattern is associated with faster recovery and more adaptive responding to negative and/or stressful events – i.e., higher flexibility, stress reduction [33,35,51,52]. Clearly, love could account for such phenomena as well (see above). Taken together, CNS activation patterns related to positive effects and love are not equally shared between the two hemispheres. Deactivations are also of interest, since emotions are likely to be the product of both increases and decreases of activities in specialized regions [10]. An overall but slight decrease in right hemisphere activity, i.e., asymmetry, particularly in prefrontal and limbic regions (including amygdala), can be stated for love [10]. However, these results may be due to different neuroimaging techniques utilized and they should be interpreted with great care. 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.

Researchers have hypothesized that pleasurable experiences like various complementary medical

treatments (e.g., therapies that elicit pleasurable sensations such as massage or acupuncture) may exert calming effects via release of gamma-aminobutyric acid (GABA) in the amygdala and other limbic areas [23,54]. This speculative aspect may be supported by the findings that link endogenous morphine production to limbic structures and complementary medicine [54]. Thus, on the neurochemical level, love and pleasure may involve substances that possess calming and anxiolytic capacities, including oxytocin, thereby facilitating feelings of well-being and relaxation [54,57,159, 197, 217]. In addition, the pleasure of love may possess a co-ordinating influence on a network of cortical or subcortical limbic and paralimbic structures, regions that are intimately involved in the regulation of cognition, emotion, and autonomic, endocrine or vegetative functions [54]. Modulation of this neuronal network could initiate a sequence of effects through which pleasurable activities regulate multisystem functions [54,57]. Moreover, NO, endocannabinoid or endorphin, and even endogenous morphine autoregulatory signaling have been demonstrated or discussed in association with pleasure-related experiences or therapies [52,54, 90,95,114,115,122, 147,182,186,215]. These molecules that possess a strong CNS affinity and are further capable of reducing stress may also be involved in the placebo response, thus promoting beneficial effects associated with love[179].

Both the amygdala and the hippocampus contain numerous receptors for varying neurotransmitters. Nuclei of the amygdala, for example, are strongly modulated by dopamine, norepinephrine, and serotonin, each of which have been demonstrated to exert their effects via NO [22,57,94,174]. Clearly, the amygdala is intimately involved in sex and sexuality, as described [159]. The medial part of the female amygdala plays an important role in pregnancy and related coordination of the endocrine system [159]. Stimulation of the corticomedial amygdala has been shown to induce ovulation in the female, and cutting the limbic stria terminalis abolishes this effect [159]. The introduction of tract lesions to the rat amygdala can eliminate male libido, but not female [120,150,174]. In general, stimulation of the amygdala may produce sexual arousal and erection, as well as representations and memories of intercourse or orgasm [91,159,174,194]. Moreover, both limbic tissues, amygdala and hippocampus, contain high concentrations of receptors for endocannabinoids and endogenous morphine [13,176]. This morphine, given its endogenous synthesis in the regions of interest for our hypothesis (see above), may activate pleasure pathways via NO [29,38,159,192,217]. Now we better understand some of the pleasurable aspects of sexual activities that may exhibit morphine-like properties and may be mediated, among others, via these endocannabinoid- and morphine-laden limbic pathways [54,159,182,217]. Finally, estrogen further stimulates NO release in the amygdala and may therefore provide an additional pathway by which the brain – and the body, organism – can down regulate immunocyte and vascular function in women [159,178]. This can be beneficial due to both the immune and the vascular trauma associated with cyclic reproductive activities, such as endometrial build-up, when a high degree of vascular and immune activities occurs [159]. Given the extent of proliferative growth capacity during peak estrogen levels in the cycle, NO may function to enhance down regulation of the immune system to allow for these changes [159]. Also, enhanced constitutive NO activity may exert beneficial effects on mental states, since it helps to keep or facilitate a state of calmness and contentment, again resembling morphine signaling [54,57,59]. Taken together, these love-related signaling molecules have the potential to make one feel 'good and relaxed' by releasing NO [159,188]. However, NO autoregulatory signaling is a crucial and common pathway in a multitude of physiological processes, including stress and placebo, as well as relaxation response [52,55,58,59,60,186]. Clearly, NO signaling is a physiologically complex phenomenon and its involvement in love and related states, as discussed here, has to be examined further.

Recent studies revealed a pathway for 'limbic touch' [10] 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 [134]. 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 [10,76]. 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 [10]. These results also pointed towards a more pronounced ('acute') physiology in romantic love, as compared to maternal, thereby demonstrating the stressful conditions involved when falling in love, i.e., arousal (see above). Thus, not all forms of positive social contact that possibly induce pleasure or well-being are automatically and neurobiologically the same, outright. For example, friendship and love share common CNS features, even in physiology. However, they are not the same: Friendship, in general, seems not to be coupled to love, that is, friendship shows distinct neural and neuroanatomic activity patterns – and vice versa [10]. 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.

Love activates specific regions in the reward system, as described above, and includes a suppression of activity in neural pathways associated with the critical social assessment of other people and with negative emotions [10]. In particular, love – and other states that involve robust reward signaling – reduces the ability to critically judge [10], i.e., impaired emotional judgment [5], decreases fear [10], and lessens the assessment

of social trustworthiness [211]. Additionally, love-pleasure-related activation/deactivation patterns of lateral prefrontal cortices lead to reduced depression and enhanced mood, i.e., 'happiness' [35,124]. Clearly, once one has become closely familiar with a person, the need to assess the social validity of that person is reduced [10]. These findings therefore may help to explain why 'love makes blind' [10], 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 [89,144]. 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 [10,57].

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 [54,57]. 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), involving hippocampal mechanisms [57,60]. 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 [60,72]. 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 [55,56,58,59,60,182, 206]. Since love and pleasure may enhance positive or healthy behaviors and beneficial motivations by their rewarding capacities, love can be 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 [54,57,159, 217]. 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 [57,133,144], 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 and attachment behaviors [26, 51,52,55,58,60].

Taken together, 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 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'.

CONCLUSIONS

Love is a complex neurobiological phenomenon, relying on trust and belief as well as brain reward activity, i.e., limbic processes. These processes critically involve oxytocin, vasopressin, dopamine, and serotoninergic signaling. Moreover, endorphin and endogenous morphinergic mechanisms, coupled to nitric oxide autoregulatory pathways, play a role. Naturally rewarding or pleasurable activities are necessary for survival and appetitive motivation, usually governing beneficial biological behaviors like eating, sex, and reproduction. Thus, love and its rewarding pleasure are much needed.

Love and social bonding employ a push-pull mechanism that activates reward and motivation pathways. Simultaneously, brain circuits that facilitate critical social assessment and negative emotions, as well as physical and mental stress, or "cognitive dwelling" (i.e., 'cognitive constipation' [179]), get down regulated. This down regulating property of love may also include further physiological phenomena. However, early phases of love, such as falling in love and its related arousal and more pronounced behaviors and molecular signaling activities, are distinct from later stages or even long-lasting relationships. Nonetheless, a broad basis of common signaling and beneficial neurobiological features exist with connection to the love concept, thereby combining physiological aspects related to maternal, romantic or sexual love, and attachment, with other healthy activities and neurobiological states. Medicine can make use of this concept, i.e., mind/body or integrative medicine.

Many questions remain open. For example, would acute exposure to oxytocin promote a search for social contact, while chronic exposure might trigger social satiety or safety and reduce social motivation? What about the other signaling pathways and neuropeptides? We attempted to answer some of theses questions on possible solutions for related medical problems or

applications. Undoubtedly, love, pleasure and lust, have a stress-reducing and health-promoting potential.

Acknowledgements

This report was in part sponsored by MH 47392, DA 09010 and the Kiernan Wellness Center. We are deeply indebted to Ms. Danielle Benz for her expertise in the preparation of this manuscript.

REFERENCES

1 Longman Dictionary of Contemporary English. Second ed. Berlin: Langenscheidt; 1987.
2 Methods of Assessing the Reinforcing Properties of Abused Drugs. New York: Springer-Verlag; 1987.
3 Acher R. Molecular evolution of fish neurohypophysial hormones: neutral and selective evolutionary mechanisms. Gen Comp Endocrinol 1996; **102**:157–72.
4 Adler L, Wedekind D, Pilz J, Weniger G, Huether G. Endocrine correlates of personality traits: a comparison between emotionally stable and emotionally labile healthy young men. Neuropsychobiology 1997; **35**:205–10.
5 Adolphs R, Tranel D, Damasio AR. The human amygdala in social judgment. Nature 1998; **393**:470–4.
6 Altenmuller EO. How many music centers are in the brain? Ann N Y Acad Sci 2001; **930**:273–80.
7 Altenmuller EO. [Apollo in us: How the brain processes music]. Musikphysiol Musikermed 2002; **9**:24.
8 Arnow BA, Desmond JE, Banner LL, Glover GH, Solomon A, Polan ML et al. Brain activation and sexual arousal in healthy, heterosexual males. Brain 2002; **125**:1014–23.
9 Barberis C, Tribollet E. Vasopressin and oxytocin receptors in the central nervous system. Crit Rev Neurobiol 1996; **10**:119–54.
10 Bartels A, Zeki S. The neural correlates of maternal and romantic love. Neuroimage 2004; **21**:1155–66.
11 Bedaux B, Cooke B. Sociobiology and the Arts. Amsterdam: 1999.
12 Bianchi E, Alessandrini C, Guarna M, Tagliamonte A. Endogenous codeine and morphine are stored in specific brain neurons. Brain Res 1993; **627**:210–5.
13 Bianchi E, Guarna M, Tagliamonte A. Immunocytochemical localization of endogenous codeine and morphine. Adv Neuroimmunol 1994; **4**:83–92.
14 Blood AJ, Zatorre RJ. Intensely pleasurable responses to music correlate with activity in brain regions implicated in reward and emotion. Proc Natl Acad Sci U S A 2001; **98**:11818–23.
15 Bozarth MA. Ventral tegmental reward system. In: Oreland L, Engel J, editors. Brain reward systems and abuse. New York: Raven Press; 1987.
16 Bozarth MA. The mesolimbic dopamine system as a model reward system. In: Willner P, Scheel-Krüger J, editors. The Mesolimbic Dopamine System: From Motivation to Action. London: Wiley & Sons; 1991.
17 Bozarth MA. Pleasure systems in the brain. In: Wartburton DM, editors. Pleasure: The politics and the reality. New York: Wiley & Sons; 1994.
18 Breiter HC, Rosen BR. Functional magnetic resonance imaging of brain reward circuitry in the human. Ann N Y Acad Sci 1999; **877**: 523–47.
19 Bridges RS. Endocrine regulation of parental behavior in rodents. In: Krasnegor NA, Bridges RS, editors. Mammalian Parenting. New York: Oxford University Press; 1990.
20 Buijs RM. Vasopressinergic and oxytocinergic pathways, synapses and central release. In: Baertschi AJ, Dreifuss JJ, editors. Neuroendocrinology of Vasopressin, Corticoliberon and Opiomelanocortin. London: Academic Press; 1982.
21 Cadet P, Mantione KJ, Stefano GB. Molecular identification and functional expression of mu3, a novel alternatively spliced variant of the human mu opiate receptor gene. Journal of Immunology 2003; **170**:5118–23.
22 Cadet P, Zhu W, Mantione K, Rymer M, Dardik I, Reisman S et al. Cyclic exercise induces anti-inflammatory signal molecule increases in the plasma of Parkinson's patients. Int J Mol Med 2003; **12**:485–92.
23 Campbell A. The limbic system and emotion in relation to acupuncture. Acupuncture in Medicine 1999; **17**:124–8.
24 Cardinale GJ, Donnerer J, Finck AD, Kantrowitz JD, Oka K, Spector S. Morphine and codeine are endogenous components of human cerebrospinal fluid. Life Sci 1987; **40**:301–6.
25 Carter CS. Oxytocin and sexual behavior. Neurosci Biobehav Rev 1992; **16**:131–44.
26 Carter CS. Neuroendocrine perspectives on social attachment and love. Psychoneuroendocrinology 1998; **23**:779–818.
27 Carter CS, Altemus M. Integrative functions of lactational hormones in social behavior and stress management. Ann N Y Acad Sci 1997; **807**:164–74.
28 Carter CS, DeVries AC, Getz LL. Physiological substrates of mammalian monogamy: the prairie vole model. Neurosci Biobehav Rev 1995; **19**:303–14.
29 Castellano C, Rossi-Arnaud C, Cestari V, Costanzi M. Cannabinoids and memory: animal studies. Curr Drug Targets CNS Neurol Disord 2003; **2**:389–402.
30 Chiodera P, Salvarani C, Bacchi-Modena A, Spallanzani R, Cigarini C, Alboni A et al. Relationship between plasma profiles of oxytocin and adrenocorticotropic hormone during suckling or breast stimulation in women. Horm Res 1991; **35**:119–23.
31 Crews D. The evolutionary antecedents to love. Psychoneuroendocrinology 1998; **23**:751–64.
32 Curtis JT, Wang Z. The neurochemistry of pair bonding. Current Directions in Psychological Science 2003; **12**:49–53.
33 Davidson RJ. Affective style, psychopathology, and resilience: Brain mechanisms and plasticity. Am Psychol 2000; **55**:1196–214.
34 Davidson RJ, Irwin W. The functional neuroanatomy of emotion and affective style. Trends Cogn Sci 1999; **3**:11–21.
35 Davidson RJ, Kabat-Zinn J, Schumacher J, Rosenkranz M, Muller D, Santorelli SF et al. Alterations in brain and immune function produced by mindfulness meditation. Psychosom Med 2003; **65**: 564–70.
36 de la Fuente-Fernandez R, Schulzer M, Stoessl AJ. The placebo effect in neurological disorders. Lancet Neurol 2002; **1**:85–91.
37 de la Fuente-Fernandez R, Stoessl AJ. The placebo effect in Parkinson's disease. Trends Neurosci 2002; **25**:302–6.
38 de la Torre JC, Pappas BA, Prevot V, Emmerling MR, Mantione K, Fortin T et al. Hippocampal nitric oxide upregulation precedes memory loss and A beta I-40 accumulation after chronic brain hypoperfusion in rats. Neurological Research 2003; **25**:635–41.
39 De Vries GJ, Villalba C. Brain sexual dimorphism and sex differences in parental and other social behaviors. Ann N Y Acad Sci 1997; **807**:273–86.
40 de Wied D, Diamant M, Fodor M. Central nervous system effects of the neurohypophyseal hormones and related peptides. Front Neuroendocrinol 1993; **14**:251–302.
41 DeVries AC, Cho MM, Cardillo S, Carter CS. Oxytocin can suppress the HPA axis in prairie voles. Soc Neurosci Abstr 1997; **22**:1851.
42 DeVries AC, DeVries MB, Taymans S, Carter CS. Modulation of pair bonding in female prairie voles (Microtus ochrogaster) by corticosterone. Proc Natl Acad Sci U S A 1995; **92**:7744–8.
43 DeVries AC, DeVries MB, Taymans SE, Carter CS. The effects of stress on social preferences are sexually dimorphic in prairie voles. Proc Natl Acad Sci U S A 1996; **93**:11980–4.
44 Donnerer J, Cardinale G, Coffey J, Lisek CA, Jardine I, Spector S. Chemical characterization and regulation of endogenous morphine and codeine in the rat. J Pharmacol Exp Ther 1987; **242**: 583–7.
45 Donnerer J, Oka K, Brossi A, Rice KC, Spector S. Presence and formation of codeine and morphine in the rat. Proc Natl Acad Sci USA 1986; **83**:4566–7.
46 Eibl K. Adaptationen im Lustmodus: Ein uebersehener Evolutionsfaktor. In: Zymner R, Engel M, editors. Anthropologie der iteratur. Poetogene Strukturen und aesthetisch-soziale Handlungsfelder. Paderborn: Mentis; 2003.
47 Elliott R, Newman JL, Longe OA, Deakin JF. Differential response patterns in the striatum and orbitofrontal cortex to financial reward in humans: a parametric functional magnetic resonance imaging study. J Neurosci 2003; **23**:303–7.
48 Esch T. [Health in stress: Change in the stress concept and its significance for prevention, health and life style]. Gesundheitswesen 2002; **64**:73–81.

49 Esch T. Musical healing in mental disorders. In: Stefano GB, Bernstein SR, Kim M, editors. Musical healing. Warsaw: Medical Science International; 2003.
50 Esch T. [Music medicine: Music in association with harm and healing]. Musikphysiol Musikermed 2003; **10**:213–24.
51 Esch T. [Stress, adaptation, and self-organization: balancing processes facilitate health and survival]. Forsch Komplementarmed Klass Naturheilkd 2003; **10**:330–41.
52 Esch T, Fricchione GL, Stefano GB. The therapeutic use of the relaxation response in stress-related diseases. Medical Science Monitor 2003; **9**:RA23–RA34.
53 Esch T, Guarna M, Bianchi E, Stefano GB. Meditation and limbic processes. Biofeedback 2004; **32**:22–7.
54 Esch T, Guarna M, Bianchi E, Zhu W, Stefano GB. Commonalities in the central nervous system's involvement with complementary medical therapies: Limbic morphinergic processes. Medical Science Monitor 2004; **10**:MS6–MS17.
55 Esch T, Stefano GB. An overview of stress and its impact in immunological diseases. Modern Aspects of Immunobiology 2002; **2**:187–92.
56 Esch T, Stefano GB. Proinflammation: A common denominator or initiator of different pathophysiological disease processes. Medical Science Monitor 2002; **8**:1–9.
57 Esch T, Stefano GB. The neurobiology of pleasure, reward processes, addiction and their health implications. Neuroendocrinology Letters 2004; **25**:235–51.
58 Esch T, Stefano GB, Fricchione GL, Benson H. Stress in cardiovascular diseases. Medical Science Monitor 2002; **8**:RA93–RA101.
59 Esch T, Stefano GB, Fricchione GL, Benson H. Stress-related diseases: A potential role for nitric oxide. Medical Science Monitor 2002; **8**:RA103–RA118.
60 Esch T, Stefano GB, Fricchione GL, Benson H. The role of stress in neurodegenerative diseases and mental disorders. Neuroendocrinology Letters 2002; **23**:199–208.
61 Ferris CF, Snowdon CT, King JA, Duong TQ, Ziegler TE, Ugurbil K et al. Functional imaging of brain activity in conscious monkeys responding to sexually arousing cues. Neuroreport 2001; **12**: 2231–6.
62 Fisher HE. Anatomy of Love. New York: Fawcett Columbine; 1992.
63 Francis S, Rolls ET, Bowtell R, McGlone F, O'Doherty J, Browning A et al. The representation of pleasant touch in the brain and its relationship with taste and olfactory areas. Neuroreport 1999; **10**:453–9.
64 Fricchione GL, Mendoza A, Stefano GB. Morphine and its psychiatric implications. Adv Neuroimmunol 1994; **4**:117–32.
65 Fricchione GL, Stefano GB. Placebo neural systems: Nitric oxide, morphine and the dopamine brain reward and motivation circuitries. Medical Science Monitor 2005; **11**:MS54–MS65.
66 Giammanco M, Tabacchi G, Giammanco S, Di Majo D, La Guardia M. Testosterone and aggressiveness. Med Sci Monit 2005; **11**: RA136–RA145.
67 Gingrich BS, Huot RL, Wang Z, Insel TR. Differential Fos expression following microinjection of oxytocin or vasopressin in the prairie vole brain. Ann N Y Acad Sci 1997; **807**:504–5.
68 Gintzler AR, Levy A, Spector S. Antibodies as a means of isolating and characterizing biologically active substances: Presence of a non-peptide morphine-like compound in the central nervous system. Proc Natl Acad Sci USA 1976; **73**:2132–6.
69 Goldstein RZ, Volkow ND. Drug addiction and its underlying neurobiological basis: neuroimaging evidence for the involvement of the frontal cortex. Am J Psychiatry 2002; **159**:1642–52.
70 Gorski RA. Structural and sexual dimorphisms in the brain. In: Krasnegor NA, Bridges RS, editors. Mammalian Parenting: Biochemical, neurobiological and behavioral determinants. New York: Oxford University Press; 1990.
71 Grazzini E, Guillon G, Mouillac B, Zingg HH. Inhibition of oxytocin receptor function by direct binding of progesterone. Nature 1998; **392**:509–12.
72 Guarna M, Ghelardini C, Galeotti N, Bartolini A, Noli L, Neri C et al. Effects of endogenous morphine deprivation on memory retention of passive avoidance learning in mice. Int J Neuropsychopharmacol 2004; **7**:311–9.
73 Guarna M, Ghelardini C, Galeotti N, Stefano GB, Bianchi E. Neurotransmitter role of endogenous morphine in CNS. Medical Science Monitor 2005; **11**:RA190–RA193.
74 Guarna M, Neri C, Petrioli F, Bianchi E. Potassium-induced release of endogenous morphine form rat brain slices. J Neurochem 1998; **70**:147–52.
75 Hamilton ME, Bozarth MA. Feeding elicited by dynorphin (1–13) microinjections into the ventral tegmental area in rats. Life Sci 1988; **43**:941–6.
76 Harlow CM. Learning to Love: The selected papers of HF Harlow. New York: Praeger; 1986.
77 Hatfield E. Love, Sex and Intimacy. New York: Harper Collins; 1993.
78 Heaton JP, Adams MA. Update on central function relevant to sex: remodeling the basis of drug treatments for sex and the brain. Int J Impot Res 2003; **15** Suppl 5:S25–S32.
79 Hennessy MB. Hypothalamic-pituitary-adrenal responses to brief social separation. Neurosci Biobehav Rev 1997; **21**:11–29.
80 Herman BH, Panksepp J. Effects of morphine and naloxone on separation distress and approach attachment: evidence for opiate mediation of social affect. Pharmacol Biochem Behav 1978; **9**:213–20.
81 Hinde RA. Biological Bases of Human Social Behavior. New York: McGraw-Hill; 1974.
82 Holstege G. Some anatomical observations on the projections from the hypothalamus to brainstem and spinal cord: an HRP and autoradiographic tracing study in the cat. Journal of Comparative Neurology 1987; **260**:98–126.
83 Holstege G, Meiners L, Tan K. Projections of the bed nucleus of the stria terminalis to the mesencephalon, pons, and medulla oblongata in the cat. Experimental Brain Research 1985; **58**:379–91.
84 Hopkins DA. Amygdalotegmentalprojections in the rat, cat and rhesus monkey. Neurosci Lett 1975; **1**:263–70.
85 Huether G. Biologie der Angst. Wie aus Stress Gefuehle werden. Goettingen: 2001.
86 Hui KKS, Liu J, Makris N, Gollub RL, Chen AJW, Moore CI et al. Acupuncture modulates the limbic system and subcortical gray structures of the human brain: Evidence from fMRI studies in normal subjects. Human Brain Mapping 2000; **9**:13–25.
87 Insel TR, Shapiro LE. Oxytocin receptor distribution reflects social organization in monogamous and polygamous voles. Proc Natl Acad Sci U S A 1992; **89**:5981–5.
88 Insel TR, Young L, Wang Z. Molecular aspects of monogamy. Ann N Y Acad Sci 1997; **807**:302–16.
89 Insel TR, Young LJ. The neurobiology of attachment. Nat Rev Neurosci 2001; **2**:129–36.
90 Jang MH, Shin MC, Kim YP, Kim EH, Kim CJ. Effect of acupuncture on nitric oxide synthase expression in cerebral cortex of streptozotocin-induced diabetic rats. Acupunct Electrother Res 2003; **28**:1–10.
91 Janszky J, Szucs A, Halasz P, Borbely C, Hollo A, Barsi P et al. Orgasmic aura originates from the right hemisphere. Neurology 2002; **58**:302–4.
92 Jenkins JS, Ang VT, Hawthorn J, Rossor MN, Iversen LL. Vasopressin, oxytocin and neurophysins in the human brain and spinal cord. Brain Res 1984; **291**:111–7.
93 Johnson AE. The regulation of oxytocin receptor binding in the ventromedial hypothalamic nucleus by gonadal steroids. Ann N Y Acad Sci 1992; **652**:357–73.
94 Joseph JT, Cardozo DL. Functional Neuroanatomy: An interactive text and manual. New York: Wiley-Liss; 2004.
95 Kaptchuk TJ. Acupuncture: theory, efficacy, and practice. Ann Intern Med 2002; **136**:374–83.
96 Karama S, Lecours AR, Leroux JM, Bourgouin P, Beaudoin G, Joubert S et al. Areas of brain activation in males and females during viewing of erotic film excerpts. Hum Brain Mapp 2002; **16**: 1–13.
97 Kawabata H, Zeki S. Neural correlates of beauty. J Neurophysiol 2004; **91**:1699–705.
98 Kendrick KM. Oxytocin, motherhood and bonding. Exp Physiol 2000; **85** Spec No:111S–24S.
99 Keverne EB, Kendrick KM. Oxytocin facilitation of maternal behavior in sheep.Ann N Y Acad Sci 1992; **652**:83–101.
100 Keverne EB, Martensz ND, Tuite B. Beta-endorphin concentrations in cerebrospinal fluid of monkeys are influenced by grooming relationships. Psychoneuroendocrinology 1989; **14**: 155–61.
101 Keverne EB, Nevison CM, Martel FL. Early learning and the social bond. Ann N Y Acad Sci 1997; **807**:329–39.

102 Knutson B, Adams CM, Fong GW, Hommer D. Anticipation of increasing monetary reward selectively recruits nucleus accumbens. J Neurosci 2001; **21**:RC159.
103 Kodaira H, Listek CA, Jardine I, Arimura A, Spector S. Identification of the convusant opiate thebaine in the mammalian brain. Proc Natl Acad Sci,USA 1989; **86**:716–9.
104 Kodaira H, Spector S. Transformation of thebaine to oripavine, codeine, and morphine by rat liver, kidney, and brain microsomes. Proceedings of the National Academy of Sciences of the United States of America 1988; **85**:1267–71.
105 Komisaruk BR, Whipple B. Love as sensory stimulation: physiological consequences of its deprivation and expression. Psychoneuroendocrinology 1998; **23**:927–44.
106 Kovacs GL, Sarnyai Z, Szabo G. Oxytocin and addiction: a review. Psychoneuroendocrinology 1998; **23**:945–62.
107 Landgraf R, Neumann I, Pittman QJ. Septal and hippocampal release of vasopressin and oxytocin during late pregnancy and parturition in the rat. Neuroendocrinology 1991; **54**:378–83.
108 Legros JJ. Inhibitory effect of oxytocin on corticotrope function in humans: are vasopressin and oxytocin ying-yang neurohormones? Psychoneuroendocrinology 2001; **26**:649–55.
109 Levine S, Lyons DM, Schatzberg AF. Psychobiological consequences of social relationships. Ann N Y Acad Sci 1997; **807**:210–8.
110 Liberzon I, Young EA. Effects of stress and glucocorticoids on CNS oxytocin receptor binding. Psychoneuroendocrinology 1997; **22**:411–22.
111 Loup F, Tribollet E, Dubois-Dauphin M, Dreifuss JJ. Localization of high-affinity binding sites for oxytocin and vasopressin in the human brain. An autoradiographic study. Brain Res 1991; **555**: 220–32.
112 Lown B, DeSilva RA. Roles of psychologic stress and autonomic nervous system changes in provocation of ventricular premature complexes. American Journal of Cardiology 1978; **41**:979–85.
113 Lown B, Verrier RL. Neural activity and ventricular fibrillation. New England Journal of Medicine 1976; **294**:1165–70.
114 Lund I, Yu LC, Uvnas-Moberg K, Wang J, Yu C, Kurosawa M et al. Repeated massage-like stimulation induces long-term effects on nociception: contribution of oxytocinergic mechanisms. Eur J Neurosci 2002; **16**:330–8.
115 Ma SX. Enhanced nitric oxide concentrations and expression of nitric oxide synthase in acupuncture points/meridians. J Altern Complement Med 2003; **9**:207–15.
116 MacDonald AW, III, Cohen JD, Stenger VA, Carter CS. Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. Science 2000; **288**:1835–8.
117 Marazziti D, Canale D. Hormonal changes when falling in love. Psychoneuroendocrinology 2004; **29**:931–6.
118 Marazziti D, Cassano GB. The neurobiology of attraction. J Endocrinol Invest 2003; **26**:58–60.
119 Mayberg HS, Silva JA, Brannan SK, Tekell JL, Mahurin RK, McGinnis S et al. The functional neuroanatomy of the placebo effect. Am J Psychiatry 2002; **159**:728–37.
120 McClure EB, Monk CS, Nelson EE, Zarahn E, Leibenluft E, Bilder RM et al. A developmental examination of gender differences in brain engagement during evaluation of threat. Biol Psychiatry 2004; **55**:1047–55.
121 Meisel RL, Sachs BD. The physiology of male sexual behavior. In: Knobil E, Neill D, editors. The Physiology of Reproduction. New York: Raven Press; 1994.
122 Meissner W, Weiss T, Trippe RH, Hecht H, Krapp C, Miltner WH. Acupuncture decreases somatosensory evoked potential amplitudes to noxious stimuli in anesthetized volunteers. Anesth Analg 2004; **98**:141–7, table.
123 Mendoza SP, Mason WA. Attachment relationships in New World primates. Ann N Y Acad Sci 1997; **807**:203–9.
124 Menkes DL, Bodnar P, Ballesteros RA, Swenson MR. Right frontal lobe slow frequency repetitive transcranial magnetic stimulation (SF r-TMS) is an effective treatment for depression: a case-control pilot study of safety and efficacy. J Neurol Neurosurg Psychiatry 1999; **67**:113–5.
125 Milgram NA. Stress and Coping in Time of War: Generalizations from the Israeli experience. New York: Brunner Mazel; 1986.
126 Miller RJ, Pickel VM. The distribution and functions of the enkephalins. J Histochem Cytochem 1980; **28**:903–17.
127 Miranda-Paiva CM, Ribeiro-Barbosa ER, Canteras NS, Felicio LF. A role for the periaqueductal grey in opioidergic inhibition of maternal behaviour. Eur J Neurosci 2003; **18**:667–74.
128 Mitchell JB, Stewart J. Facilitation of sexual behaviors in the male rat associated with intra-VTA injections of opiates. Pharmacol Biochem Behav 1990; **35**:643–50.
129 Moles A, Kieffer BL, D'Amato FR. Deficit in attachment behavior in mice lacking the mu-opioid receptor gene. Science 2004; **304**: 1983–6.
130 Nestler EJ, Malenka RC, Hyman SE. Molecular basis of neuropharmacology. Columbus: McGraw-Hill; 2001.
131 Nestler EJ. Molecular basis of long-term plasticity underlying addiction. Nat Rev Neurosci 2001; **2**:119–28.
132 Nestler EJ, Malenka RC. The addicted brain. Sci Am 2004; **290**: 78–85.
133 Numan M, Sheehan TP. Neuroanatomical circuitry for mammalian maternal behavior. Ann N Y Acad Sci 1997; **807**:101–25.
134 Olausson H, Lamarre Y, Backlund H, Morin C, Wallin BG, Starck G et al. Unmyelinated tactile afferents signal touch and project to insular cortex. Nat Neurosci 2002; **5**:900–4.
135 Olds J. Drives and reinforcements: Behavioral studies of hypothalamic functions. New York: Raven Press; 1977.
136 Olds J, MILNER P. Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain. J Comp Physiol Psychol 1954; **47**:419–27.
137 Onions CT. The Oxford Dictionary of English Etymology. New York: Oxford University Press; 1966.
138 Ostrowski NL. Oxytocin receptor mRNA expression in rat brain: implications for behavioral integration and reproductive success. Psychoneuroendocrinology 1998; **23**:989–1004.
139 Panksepp J, Liviy SM, Normansell LA. Brain Opioids and Social Emotions. In: Reite M, Field T, editors. The Psychobiology of Attachment and Separation. New York: Academic Press; 1985.p.1–49.
140 Panksepp J, Nelson E, Bekkedal M. Brain systems for the mediation of social separation-distress and social-reward. Evolutionary antecedents and neuropeptide intermediaries. Ann N Y Acad Sci 1997; **807**:78–100.
141 Panksepp J, Nelson E, Siviy S. Brain opioids and mother-infant social motivation. Acta Paediatr Suppl 1994; **397**:40–6.
142 Patchev VK, Almeida OF. Corticosteroid regulation of gene expression and binding characteristics of vasopressin receptors in the rat brain. Eur J Neurosci 1995; **7**:1579–83.
143 Patchev VK, Schlosser SF, Hassan AH, Almeida OF. Oxytocin binding sites in rat limbic and hypothalamic structures: site-specific modulation by adrenal and gonadal steroids. Neuroscience 1993; **57**:537–43.
144 Pedersen CA. Oxytocin control of maternal behavior. Regulation by sex steroids and offspring stimuli. Ann N Y Acad Sci 1997; **807**: 126–45.
145 Pfaff DW, Schwartz-Giblin S, McCarthy MM, Kow LM. Cellular and molecular mechanisms of female reproductive behaviors. In: Knobil E, Neill D, editors. The Physiology of Reproduction. New York: Raven Press; 1994.
146 Pinker S. Wie das Denken im Kopf entsteht. Muenchen: 1998.
147 Piotrowski MM, Paterson C, Mitchinson A, Kim HM, Kirsh M, Hinshaw DB. Massage as adjuvant therapy in the management of acute postoperative pain: a preliminary study in men. J Am Coll Surg 2003; **197**:1037–46.
148 Poeaknapo C, Schmidt J, Brandsch M, Drager B, Zenk MH. Endogenous formation of morphine in human cells. Proc Natl Acad Sci U S A 2004; **101**:14091–6.
149 Porges SW. Love: an emergent property of the mammalian autonomic nervous system. Psychoneuroendocrinology 1998; **23**: 837–61.
150 Rasia-Filho AA, Fabian C, Rigoti KM, Achaval M. Influence of sex, estrous cycle and motherhood on dendritic spine density in the rat medial amygdala revealed by the Golgi method. Neuroscience 2004; **126**:839–47.
151 Rauch SL, Shin LM, Dougherty DD, Alpert NM, Orr SP, Lasko M et al. Neural activation during sexual and competitive arousal in healthy men. Psychiatry Res 1999; **91**:1–10.
152 Reite M, Boccia ML. Physiological aspects of adult attachment. In: Sperling MB, Bermann WH, editors. Attachment in Adults. New York: Guilford Press; 1994.
153 Robinson TE, Berridge KC. Incentive-sensitization and addiction. Addiction 2001; **96**:103–14.

154 Rodriguez dF, Navarro M. Role of the limbic system in dependence on drugs. Ann Med 1998; **30**:397–405.
155 Rolls ET, O'Doherty J, Kringelbach ML, Francis S, Bowtell R, McGlone F. Representations of pleasant and painful touch in the human orbitofrontal and cingulate cortices. Cereb Cortex 2003; **13**:308–17.
156 Rossetti ZL, Hmaidan Y, Gessa GL. Marked inhibition of mesolimbic dopamine release: A common feature of ethanol, morphine, cocaine and amphetamine abstinence in rats. Eur J Pharmacol 1992; **221**:227–34.
157 Ryan RM, Deci EL. Self-determination theory and the facilitation of intrinsic motivation, social development, and well-being. Am Psychol 2000; **55**:68–78.
158 Sachser N, Kaiser S. Prenatal social stress masculinizes the females' behaviour in guinea pigs. Physiol Behav 1996; **60**:589–94.
159 Salamon E, Esch T, Stefano GB. The role of the amygdala in mediating sexual and emotional behavior via coupled nitric oxide release. Acta Pharmacologica Sinica 2005; **26**:389–95.
160 Salamon E, Kim M, Beaulieu J, Stefano GB. Sound therapy induced relaxation: down regulating stress processes and pathologies. Med Sci Monit 2003; **9**:RA96–RA101.
161 Sarnyai Z, Kovacs GL. Role of oxytocin in the neuroadaptation to drugs of abuse. Psychoneuroendocrinology 1994; **19**:85–117.
162 Schacter DL. Wir sind Erinnerung. Gedaechtnis und Persoenlichkeit. Reinbek: 1999.
163 Schiffer F, Hartley LH, Schulman CL, Abelmann WH. Evidence for emotionally-induced coronary arterial spasm in patients with angina pectoris. British Heart Journal 1980; **44**:62–6.
164 Schlaepfer TE, Strain EC, Greenberg BD, Preston KL, Lancaster E, Bigelow GE et al. Site of opioid action in the human brain: mu and kappa agonists' subjective and cerebral blood flow effects. Am J Psychiatry 1998; **155**:470–3.
165 Schultz W. Multiple reward signals in the brain. Nat Rev Neurosci 2000; **1**:199–207.
166 Schumacher M, Coirini H, Pfaff DW, McEwen BS. Behavioral effects of progesterone associated with rapid modulation of oxytocin receptors. Science 1990; **250**:691–4.
167 Sher L. The placebo effect on mood and behavior: possible role of opioid and dopamine modulation of the hypothalamic-pituitary-adrenal system. Forsch Komplementarmed Klass Naturheilkd 2003; **10**:61–8.
168 Shipley JT. Dictionary of Word Origins. New York: Philosophical Library; 1945.
169 Simpson JA, Rholes WS. Stress and secure base relationships in adulthood. In: Bartholomew K, Perlman D, editors. Advances in personal relationships (Vol. 5): Attachment processes in adulthood. London: Kingsley; 1994.p.181–204.
170 Slingsby BT, Stefano GB. Placebo: Harnessing the power within. Modern Aspects of Immunobiology 2000; **1**:144–6.
171 Slingsby BT, Stefano GB. The active ingredients in the sugar pill: Trust and belief. Placebo 2001; **2**:33–8.
172 Small DM, Jones-Gotman M, Dagher A. Feeding-induced dopamine release in dorsal striatum correlates with meal pleasantness ratings in healthy human volunteers. Neuroimage 2003; **19**:1709–15.
173 Small DM, Zatorre RJ, Dagher A, Evans AC, Jones-Gotman M. Changes in brain activity related to eating chocolate: From pleasure to aversion. Brain 2001; **124**:1720–33.
174 Smith CM. Elements of Molecular Neurobiology. 3rd ed. New York: Wiley-Liss; 2002.
175 Sonetti D, Peruzzi E, Stefano GB. Endogenous morphine and ACTH association in neural tissues. Medical Science Monitor 2005; **11**:MS22–MS30.
176 Spector S, Munjal I, Schmidt DE. Endogenous morphine and codeine. Possible role as endogenous anticonvulsants. Brain Res 2001; **915**:155–60.
177 Spencer H. Principles of Psychology. New York: Appleton; 1880.
178 Stefano GB. Endocannabinoid immune and vascular signaling. Acta Pharmacologica Sinica 2000; **21**:1071–81.
179 Stefano GB, Benson H, Fricchione GL, Esch T. The Stress Response: Always good and when it is bad. New York: Medical Science International; 2005.
180 Stefano GB, Cadet P, Zhu W, Rialas CM, Mantione K, Benz D et al. The blueprint for stress can be found in invertebrates. Neuroendocrinology Letters 2002; **23**:85–93.
181 Stefano GB, Digenis A, Spector S, Leung MK, Bilfinger TV, Makman MH et al. Opiatelike substances in an invertebrate, a novel opiate receptor on invertebrate and human immunocytes, and a role in immunosuppression. Proc Natl Acad Sci USA 1993; **90**: 11099–103.
182 Stefano GB, Esch T, Cadet P, Zhu W, Mantione K, Benson H. Endocannabinoids as autoregulatory signaling molecules: coupling to nitric oxide and a possible association with the relaxation response. Med Sci Monit 2003; **9**:RA63–RA75.
183 Stefano GB, Fricchione GL. The biology of deception: Emotion and morphine. Med Hypotheses 1995; **49**:51–4.
184 Stefano GB, Fricchione GL. The biology of deception: The evolution of cognitive coping as a denial-like process. Med Hypotheses 1995; **44**:311–4.
185 Stefano GB, Fricchione GL, Goumon Y, Esch T. Pain, immunity, opiate and opioid compounds and health. Medical Science Monitor 2005; **11**:MS47–MS53.
186 Stefano GB, Fricchione GL, Slingsby BT, Benson H. The placebo effect and relaxation response: Neural processes and their coupling to constitutive nitric oxide. Brain Research: Brain Research Reviews 2001; **35**:1–19.
187 Stefano GB, Goumon Y, Casares F, Cadet P, Fricchione GL, Rialas C et al. Endogenous morphine. Trends in Neurosciences 2000; **9**: 436–42.
188 Stefano GB, Prevot V, Cadet P, Dardik I. Vascular pulsations stimulating nitric oxide release during cyclic exercise may benefit health: a molecular approach (review). International Journal of Molecular Medicine 2001; **7**:119–29.
189 Stefano GB, Scharrer B. Endogenous morphine and related opiates, a new class of chemical messengers. Adv Neuroimmunol 1994; **4**:57–68.
190 Stefano GB, Scharrer B, Smith EM, Hughes TK, Magazine HI, Bilfinger TV et al. Opioid and opiate immunoregulatory processes. Crit Rev in Immunol 1996; **16**:109–44.
191 Stefano GB, Zhu W, Cadet P, Salamon E, Mantione KJ. Music alters constitutively expressed opiate and cytokine processes in listeners. Medical Science Monitor 2004; **10**:MS18–MS27.
192 Steffens M, Engler C, Zentner J, Feuerstein TJ. Cannabinoid CB1 receptor-mediated modulation of evoked dopamine release and of adenylyl cyclase activity in the human neocortex. Br J Pharmacol 2004; **141**:1193–203.
193 Sternberg RJ, Barnes MI. The Psychology of Love. New Haven: Yale University Press; 1988.
194 Tanuri FD, Thomaz RB, Tanuri JA. [Temporal lobe epilepsy with aura of pleasure. Case report]. Arq Neuropsiquiatr 2000; **58**:178–80.
195 Thompson AC, Kristal MB. Opioids in the ventral tegmental area facilitate the onset of maternal behavior in the rat. Society for Neuroscience Abstracts 1994; **18**:659.
196 Troland LT. The fundamentals of human motivation. New York: Van Nostrand Reinhold; 1928.
197 Uvnas-Moberg K. Physiological and endocrine effects of social contact. Ann N Y Acad Sci 1997; **807**:146–63.
198 Uvnas-Moberg K. Oxytocin may mediate the benefits of positive social interaction and emotions. Psychoneuroendocrinology 1998; **23**:819–35.
199 Vaccari CS, Carter CS, Ostrowski NL. Neonatal exposure to arginine vasopressin alters adult vasopressin V1a and oxytocin receptor mRNA expression in rat brain. Soc Neurosci Abstr 1996; **26**:81.
200 Vetulani J. Drug addiction. Part II. Neurobiology of addiction. Pol J Pharmacol 2001; **53**:303–17.
201 Wager TD, Rilling JK, Smith EE, Sokolik A, Casey KL, Davidson RJ et al. Placebo-induced changes in fMRI in the anticipation and experience of pain. Science 2004; **303**:1162–7.
202 Wang Z, Young LJ, Liu Y, Insel TR. Species differences in vasopressin receptor binding are evident early in development: comparative anatomic studies in prairie and montane voles. J Comp Neurol 1997; **378**:535–46.
203 Ward IL, Ward OB. Sexual behavior differentiation: Effects of prenatal manipulations in rats. In: Adler N, Pfaff D, Goy RW, editors. Handbook of Behavioral Neurobiology: Reproduction. New York: Plenum Press; 1986.
204 Weiss F, Koob GF. Drug addiction: Functional neurotoxicity of the brain reward systems. Neurotox Res 2001; **3**:145–56.
205 Wellens HJ, Vermeulen A, Durrer D. Ventricular fibrillation occurring on arousal from sleep by auditory stimuli. Circulation 1972; **46**:661–5.

206 Willett WC. Balancing life-style and genomics research for disease prevention. Science 2002; **296**:695–8.
207 Williams JR, Catania KC, Carter CS. Development of partner preferences in female prairie voles (Microtus ochrogaster): the role of social and sexual experience. Horm Behav 1992; **26**:339–49.
208 Wilson EO. On art. In: Cooke B, Turner F, editors. Biopoetics. Evolutionary explorations in the arts. Lexington: 1999.
209 Winslow JT, Hastings N, Carter CS, Harbaugh CR, Insel TR. A role for central vasopressin in pair bonding in monogamous prairie voles. Nature 1993; **365**:545–8.
210 Winslow JT, Insel TR. Effects of central vasopressin administration to infant rats. Eur J Pharmacol 1993; **233**:101–7.
211 Winston JS, Strange BA, O'Doherty J, Dolan RJ. Automatic and intentional brain responses during evaluation of trustworthiness of faces. Nat Neurosci 2002; **5**:277–83.
212 Wise RA. Catecholamine theories of reward: A critical review. Brain Res 1978; **152**:215–47.
213 Wise RA, Bozarth MA. Brain reward circuitry: Four circuit elements "wired" in apparent series. Brain Res Bull 1984; **12**:203–8.
214 Witt DM, Carter CS, Insel TR. Oxytocin receptor-binding in female prairie voles: Endogenous and exogenous oestradiol stimulation. J Neuroendocrinol 1991; **3**:155–61.
215 Yang R, Huang ZN, Cheng JS. Anticonvulsion effect of acupuncture might be related to the decrease of neuronal and inducible nitric oxide synthases. Acupunct Electrother Res 2000; **25**:137–43.
216 Zhang L, Lou D, Jiao H, Zhang D, Wang X, Xia Y et al. Cocaine-induced intracellular signaling and gene expression are oppositely regulated by the dopamine D1 and D3 receptors. J Neurosci 2004; **24**:3344–54.
217 Zhu W, Ma Y, Bell A, Esch T, Guarna M, Bilfinger TV et al. Presence of morphine in rat amygdala: Evidence for the 3 opiate receptor subtype via nitric oxide release in limbic structures. Med Sci Monit 2004; **10**:BR433–BR439.
218 Zhu W, Ma Y, Cadet P, Yu D, Bilfinger TV, Bianchi E et al. Presence of reticuline in rat brain: A pathway for morphine biosynthesis. Mol Brain Res 2003; **117**:83–90.
219 Zhu W, Mantione KJ, Shen L, Stefano GB. In vivo and in vitro L-DOPA exposure increases ganglionic morphine levels. Medical Science Monitor 2005; **11**:MS1–MS5.
220 Zitzmann M, Nieschlag E. Testosterone levels in healthy men and the relation to behavioural and physical characteristics: facts and constructs. Eur J Endocrinol 2001; **144**:183–97.