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REVIEW

LOVE IS MORE THAN JUST A KISS: A NEUROBIOLOGICAL PERSPECTIVE ON LOVE AND AFFECTION

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Abstract—Love, attachment, and truth of human monogamy have become important research themes in neuroscience. After the introduction of functional Magnetic Resonance Imaging (fMRI) and Positron Emission Tomography (PET), neuroscientists have demonstrated increased interest in the neurobiology and neurochemistry of emotions, including love and affection. Neurobiologists have studied pair-bonding mechanisms in animal models of mate choice to elucidate neurochemical mechanisms underlying attachment and showed possible roles for oxytocin, vasopressin, and dopamine and their receptors in pair-bonding and monogamy. Unresolved is whether these substances are also critically involved in human attachment. The limited number of available imaging studies on love and affection is hampered by selection bias on gender, duration of a love affair, and cultural differences. Brain activity patterns associated with romantic love, shown with fMRI, overlapped with regions expressing oxytocin receptors in the animal models, but definite proof for a role of oxytocin in human attachment is still lacking. There is also evidence for a role of serotonin, cortisol, nerve growth factor, and testosterone in love and attachment. Changes in brain activity related to the various stages of a love affair, gender, and cultural differences are unresolved and will probably become important research themes in this field in the near future. In this review we give a resume of the current knowledge of the neurobiology of love and attachment and we discuss in brief the truth of human monogamy.

Key words: brain activity, romantic love, attachment, hormones, gender differences, monogamy.

Contents

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Abbreviations: fMRI, functional magnetic resonance imaging; HPA, hypothalamic pituitary adrenal; NGF, nerve growth factor; OCD, obsessive-compulsive disorder.

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Love has been a focus of attention ever since the beginning of mankind, and it has been an important theme for artists for thousands of years, being a source of inspiration for poetry, music, literature, paintings, and many other arts for as long as they have existed. Recently, romantic love also became a topic of interest for scientists. Love has been intensely studied by psychologists and social scientists in the last century. At the beginning of the last century, researchers mainly focused on marriage and marital satisfaction (Berscheid, 2010), reflecting the important position of marriage in early 20th century society. Romantic love was seen as a main factor for "family disorganization," and thus, it should be suppressed to keep stability within the family. As research focused on how to keep families together and prevent marital dissatisfaction, conflict-solving studies prevailed, believing that this was the key to a long and happy marriage. However, these early 20th century investigators might have been wrong because recent studies indicate that conflict situations within a marriage and satisfaction with marriage are two largely unrelated factors. Instead, signs of positive affect (eye contact, cuddling, positive remarks about each other, etc.) are more important for marital satisfaction, and absence of positive affect is probably a better predictor of marital problems than conflicts (Huston et al., 2001).

During the course of the 20th century, the focus gradually shifted from marital satisfaction to romantic love. Research on romantic love focussed mainly on why people fall in love and how individuals choose a specific partner in which personality and former relationships are shown to be important factors (Berscheid, 2010; Brumbaugh and Fraley, 2006; Campbell et al., 2005). However, love remained a research field mainly for psychologists, despite the massive increase in neuroscientific research in the second half of the 20th century. This might reflect the common feeling that love is an emotion that cannot be explained by studying brain activity and that understanding neuronal corre-

lates of love will not help us to understand the whole range of aspects associated with romantic love. However, research has shown that basically every emotion has its neuronal correlates, love being no exception.

In the last few decades, an increasing number of studies has focused on the neuronal correlates of love, unraveling brain mechanisms involved in the experience of romantic love. Many studies use novel techniques such as functional Magnetic Resonance Imaging (fMRI) and Positron Emission Tomography (PET) to study the patterns of brain activity of those who are in love. Others study animal behaviors that may be related to human romantic love. When examining these studies, it is important to keep in mind that there is an important difference between the conclusions based on the biological mechanisms involved in animal pair-bonding and human romantic love in which psychological mechanisms also play an important role. Nevertheless, animal studies on pair-bonding have led to a rapid increase in knowledge about neural correlates of romantic love, although many questions remain unanswered.

In this article, we will integrate and review data from psychological studies into the current knowledge of neurobiological mechanisms underlying romantic love. We address the evolution of love and attachment, neuroendocrine factors, brain activity, and gender differences in love, and how a love relationship evolves over time. Finally, we will discuss in brief human monogamy.

LOVE IN AN EVOLUTIONARY PERSPECTIVE

It has been suggested that romantic love developed from courtship neuronal mechanisms and thus can be seen as a human form of the courtship behavior (Fisher, 1998). Indeed, courtship behavior in lower mammals shares many of the features seen in romantic love, including increased energy, focused attention, obsessive following, affiliative gestures, possessive mate guarding, and motivation to win a preferred mating partner. Both courtship attraction and romantic love are systems for mate choice, evolutionary mechanisms developed to choose a partner that offers the best chances to the offspring.

Romantic love is also part of the adult attachment system, and it seems to be essential in the early stages of attachment. The adult attachment system evolved as a system to keep parents together for the time necessary to raise the offspring (Fisher, 1998). In this context, it is interesting that monogamous (or serial monogamous) attachment seems to have mainly evolved in species in which nurturance of offspring requires the cooperation of both parents (Kleiman, 1977). In many species these bonds only last for one breeding season, although in some species life-long attachments are formed. Whether truly life-long bonds are formed in humans is still a matter of debate especially because divorce rates approach or even exceed 50% in Western societies (Kalmijn, 2007; Blow and Hartnett, 2005).

Fisher (1992) studied divorce rates in different cultures and reported a substantial increase in divorce rates in the fourth year of marriage. Based on these data, she developed her “four-year itch” theory, stating that human adult pair-bonds are formed for approximately four years, the period in which the offspring is most vulnerable. After these four years, adult pair-bonds can be resolved, allowing both parents to form attachments with other individuals. Thus, Fisher (1992) suggests that the human mating system is one of serial monogamy, not life-long attachments. In fact, it much resembles the mating systems found in several serial monogamous animals that form pair-bonds for one breeding season only. The only difference is that the duration for the offspring to become independent is much longer for humans than for lower mammals. In support of Fisher’s theory, she also found that the four years time window could be extended to about seven years if the couple has more than one child, demanding longer cooperation of the parents in the care for the second child.

Romantic love is part of the adult attachment system, which is believed to be evolved from an evolutionary much older attachment system; mother–infant attachment. Attachment bonds between mother and infant are most likely formed around the time of birth. These bonds keep mother and infant together for as long as the infant cannot function independently. Thus, adult attachment and mother–infant attachment share a functional purpose; both systems evolved to keep two individuals together for a certain period of their lives (Zeki, 2007). Furthermore, the brain circuits involved in both attachment systems are largely similar, and oxytocin and vasopressin are the major hormonal players in both attachment systems.

ENDOCRINE FACTORS IN LOVE

Like any other emotion, love is regulated by endocrine factors. Several factors have been identified as playing a role in romantic love and attachment, including oxytocin, vasopressin, dopamine, serotonin, cortisol and other stress hormones, nerve growth factor, and testosterone. This chapter will review the role of each of these factors in romantic love.

Oxytocin and vasopressin

Oxytocin and vasopressin have consistently been implicated in pair-bonding and love (Zeki, 2007). Both hormones are produced by the paraventricular and supraoptic nuclei of the hypothalamus and are released into the circulation by the pituitary gland (Debiec, 2007). Oxytocin’s principle actions are triggering muscular contractions during birth and release of milk during lactation (Zeeman et al., 1997), whereas vasopressin is important for cardiovascular function and the maintenance of blood pressure (Earley, 1966). Oxytocin and vasopressin also function as neuropeptides; small compounds that act locally within the brain on various pathways (Lim and Young, 2006). So far, one oxytocin and three vasopressin receptors have been identified. The vasopressin V2 receptor is found in the kidney, the V1b receptor in the pituitary, and the V1a receptor in the cardiovascular system and the brain (Zingg, 1996). The vasopressin V1a and oxytocin receptors are

present in many parts of the brain that are associated with love, including parts of the dopamine reward system (Bartels and Zeki, 2004). It is generally accepted that activation of this reward system is important for the formation of pair-bonds, and especially for making love a rewarding experience.

Most research on the role of vasopressin, oxytocin, and their receptors in love and pair-bonding has been performed in prairie voles; monogamous voles that live on the prairies of central North America (Aragona and Wang, 2004). After mating, prairie voles form monogamous pairs that stay together for a lifetime. These prairie voles are closely related to the promiscuous montane voles, and these two species are often compared in studies on the biological determinants of monogamous behavior and pair-bonding.

The differences in mating systems between these voles can be linked to oxytocin and vasopressin receptor expression differences (Insel and Shapiro, 1992; Young et al., 1998; Insel et al., 1994). Studies have shown that prairie voles have higher densities of oxytocin receptors in the brain than montane voles, especially in the prelimbic cortex and the nucleus accumbens, parts of the dopamine reward system, and in the lateral parts of the amygdaloid complex, which is involved in emotion-related memory formation (Insel and Shapiro, 1992; Young et al., 1998). Prairie voles have also higher vasopressin V1a receptor densities in the lateral amygdala and ventral pallidum. The latter area plays a role in motivation and is part of the dopamine reward system (Insel et al., 1994; Young et al., 2001). Montane voles, on the other hand, have a higher V1a and oxytocin receptor density in the lateral septum (Insel and Shapiro, 1992; Insel et al., 1994). These distribution differences are also seen in other monogamous and promiscuous voles (Insel and Shapiro, 1992).

When prairie voles mate, oxytocin and vasopressin are released into the brain, facilitating partner preference for the mating partner and thus instituting pair-bonding (Carter et al., 1995). When oxytocin and vasopressin release is blocked in prairie voles, these voles become promiscuous, and partner preferences are no longer present (Liu et al., 2001; Lim and Young, 2004), and when the prairie vole V1a receptor is expressed in the montane voles, these voles become monogamous and will form enduring attachments like those seen in prairie voles (Lim et al., 2004). As there is no functional difference between prairie vole and montane vole V1a receptors, differences in behavior must be induced by differences in V1a receptor distribution in the brain.

Many of the sites of increased vasopressin and oxytocin receptor density after mating in monogamous voles are part of the dopamine reward system (Lim and Young, 2004). This suggests that the monogamous behavior seen in prairie voles is at least in part induced by activation of the reward system by oxytocin and vasopressin. Indeed, the effects of oxytocin and vasopressin on attachment and pair-bonding are at least partially dopamine dependent, as dopamine antagonists can block these effects and dopamine agonists can induce partner preferences in the absence of mating (Wang et al., 1999; Gingrich et al., 2000).

Although oxytocin and vasopressin play similar roles in pair-bonding, there seem to be some differences in their effects, including sex differences and differences on amygdaloid output (Lim and Young, 2006). In male prairie voles, central infusion of vasopressin into the ventral pallidum induces partner preference, whereas infusion of a V1a receptor antagonist blocks partner preference (Lim and Young, 2004; Wang et al., 1994; Winslow et al., 1998). Oxytocin on the other hand induces partner preference in female prairie voles, but not in males, and central infusion of an oxytocin receptor antagonist into the nucleus accumbens can block partner preference in female prairie voles (Young et al., 2001; Insel and Hulihan, 1995). The exact meaning of these sex differences remains unclear, as does the question whether similar sex differences occur in human pair-bonding. Besides these sex differences, oxytocin and vasopressin have opposite effects on amygdaloid output (Debiec, 2007). Whereas oxytocin has anxiolytic and stress-reducing effects, vasopressin increases fear and stress responses and is important for aversive learning (Carrasco and Van de Kar, 2003; Holmes et al., 2003). An explanation for these differences is that vasopressin and oxytocin activate a different set of neurons within the amygdala (Debiec, 2007; Huber et al., 2005). Oxytocin receptors are mainly found in the lateral parts of the central nucleus of the amygdala (CeA), where they activate GABAergic neurons that project to medial parts of the CeA (Huber et al., 2005). This activation results in an inhibitory effect on amygdaloid output. Vasopressin, on the other hand, directly excites neurons in medial parts of the CeA, which increases amygdaloid output and fear responses (Huber et al., 2005; Debiec, 2007).

Besides stress reducing, anxiolytic, and antinociceptive effects of oxytocin, oxytocin is also known as the “trust hormone,” as it induces feelings of trust (Kéri and Kiss, 2011). Oxytocin thus helps to overcome neophobia; a probably important effect of oxytocin in the early phases of romantic love.

Dopamine

Oxytocin and vasopressin interact with the dopamine reward system and can induce release of dopamine, making love a rewarding experience (Young and Wang, 2004). The dopaminergic system and dopamine-innervated regions of species that form pair-bonds contain a high density of oxytocin and vasopressin receptors (Bartels and Zeki, 2004), especially the nucleus accumbens, the ventral tegmental area, the paraventricular hypothalamic nucleus, and the prefrontal cortex, making these regions highly responsive to changes in central levels of oxytocin and vasopressin.

It has been shown that the release of dopamine in the nucleus accumbens plays a central role in the generation of monogamous pair-bonds in prairie voles (Aragona et al., 2003). Both male and female prairie voles will develop partner preference after only a single mating encounter, which is dependent upon dopamine release into the nu-

cleus accumbens and its effect on the dopamine D2 receptor. Infusion of a D2 receptor agonist into the nucleus accumbens induces partner preferences in male prairie voles even after a short encounter that does not include copulation, whereas the infusion of D2 receptor antagonists prevents the voles from developing partner preferences after mating, despite the presence of oxytocin (Gingrich et al., 2000). Stimulation of the D1 receptor has the opposite effect and blocks the formation of pair-bonds, whereas D2 receptor activation facilitates partner preference (Aragona et al., 2003).

Infusions of moderate doses of dopamine into the nucleus accumbens facilitate pair-bonding, whereas infusion of high doses does not generate this effect (Aragona et al., 2003; Edwards and Self, 2006). This observation is because of dopamine's higher affinity for the D2 receptor than for the D1 receptor (Seeman and Van Tol, 1994), in which binding to the D2 receptor stimulates pair-bonding. Moreover, Aragona et al. (2003) showed that after the formation of a pair-bond, D1 receptor density in the nucleus accumbens is upregulated. They hypothesized that this upregulation prevents the formation of new pair-bonds and thereby maintains stability of the existing bond. In support of this hypothesis, they showed that infusion of a D1 receptor antagonist into the nucleus accumbens of male prairie voles prevents aggression toward female strangers that normally occurs in pair-bonded male prairie voles. Instead, these prairie voles engaged in close contacts and even mating with female strangers (Aragona et al., 2003). Thus, the increase in D1 receptor density after pair-bond formation indeed seems to prevent the formation of new pair-bonds and maintain the existing pair-bond.

Differences in projections and functions of neurons expressing the D1 and D2 receptors in the nucleus accumbens may help explain their different actions in pair-bonding. Although D1 receptor stimulation has been shown to induce neuroplasticity and reward-related learning and memory (Beninger and Miller, 1998), D2 expressing neurons project to the ventral pallidum, an area rich in vasopressin receptors (Edwards and Self, 2006). This area integrates information from the D2-positive neurons with information from the vasopressinergic system to activate complex downstream neuronal networks that aid in the formation of pair-bonds (Edwards and Self, 2006; Young and Wang, 2004).

In many ways, love can feel like an addiction, and the dopaminergic pathways that are involved in love and pair-bond formation are largely similar to those that are involved in addictive behavior (Edwards and Self, 2006). As in pair-bonding in male prairie voles, animal studies with cocaine-addicted rats show that while the D2 receptor stimulates addictive behavior, the D1 receptor inhibits it (Self et al., 1996). It is not yet clear whether monogamous pair-bonding in female prairie voles is regulated in the same way, and it is unknown what the value of these results is for other (serial) monogamous species, including humans. Furthermore, it is likely that some of the actions of oxytocin are dopamine-dependent, and that the oxytocinergic and dopaminergic systems need to cooperate to establish successful pair-bonds. This has been demonstrated in female prairie voles, where administration of an oxytocin receptor antagonist blocks partner preference induced by D2 activation, whereas blockade of D2 receptors in the nucleus accumbens prevents partner preference formation induced by oxytocin (Young and Wang, 2004; Liu and Wang, 2003).

Serotonin

Another substance implicated in love and pair-bonding is the neurotransmitter serotonin. Levels of serotonin are inversely correlated with corticosteroid (Tafet et al., 2001). It is therefore not surprising that in early stages of romantic love, there is a depletion of serotonin levels (Zeki, 2007). Depletion of central serotonin is also found in several psychiatric disorders, including obsessive-compulsive disorder (OCD) (Micallef and Blin, 2001), depression (Young and Leyton, 2002), and anxiety disorder (Leonardo and Hen, 2006). Indeed, early stages of romantic love show similarities to OCD, including symptoms of anxiety, stress, and obtrusive thinking. It is therefore attractive to think of early love as a mild serotonin-depletion-related form of obsessive behavior, although we should keep in mind that OCD is a Diagnostic and Statistical Manual of Mental Disorders version IV (DSM-IV) disorder (Leckman et al., 2010) and the early stage of romantic love is not. Further similarities between obsessive behavior and early romantic love were elucidated by Marazziti et al. (1999), who evaluated platelet serotonin transporter levels in OCD patients and subjects who had recently fallen in love. In both groups, platelet serotonin transporter levels were decreased compared with levels in the control group. On reevaluation 12–18 months after the start of the relationship, subjects did not have any obsessive ideation regarding the partner anymore, and platelet serotonin transporter levels had gone back to control levels. Again, there is a parallel with OCD, in which platelet serotonin receptor levels normalize after successful treatment of the disorder (Delorme et al., 2004).

Finally, a serotonin 5-HT2A receptor polymorphism has recently been linked to an obsessive romantic attachment behavior (Emanuele et al., 2007), further implicating serotonin as an important factor in the obsessive component of romantic love.

Hypothalamic pituitary adrenal axis and cortisol

In early stage romantic love, the hypothalamic pituitary adrenal (HPA) axis activity is increased, as shown by Marazziti and Canale (2004). They performed an early morning experiment in which serum cortisol levels were measured in subjects who had fallen in love within the past six months (Marazziti and Canale, 2004). Interestingly, in a reevaluation experiment 12–24 months later, in which samples were collected in the early morning hours using the same procedure as in the first experiment, this increase was no longer observed. These observations indicate that increased HPA axis activity is specific to early stages romantic love.

Besides the well-known euphoric feelings in early romantic love, falling in love is also accompanied by increased levels of stress and insecurity about the beginning of the relationship. This observation of increased stress is supported by evidence of elevated cortisol levels (Marazziti and Canale, 2004). It has been hypothesized that these elevated cortisol levels are necessary to overcome initial neophobia (Marazziti and Canale, 2004). On the other hand, long-term relationships tend to decrease stress levels and increase feelings of security, accounting for a decrease in stress hormone levels and perhaps attributing to some of the health benefits of long-term relationships (Esch and Stefano, 2005). Another explanation for the increased cortisol levels is that high levels of stress and stress hormones stimulate pair-bonding and attachment (DeVries et al., 1995, 1996). Here, increased stress levels trigger the formation of pair-bonds, which in turn facilitates social support that has positive effects on plasma cortisol levels and coping with stress, particularly in females (Westenbroek et al., 2005).

The HPA axis is also under the influence of oxytocin and vasopressin (Gillies et al., 1982; Rivier and Vale, 1983; Legros, 2001). These hormones exert opposite effects on the HPA axis, with oxytocin decreasing and vasopressin increasing HPA axis activity (Legros, 2001). So although vasopressin could potentially play a role in increased HPA axis activity in the early stages of romantic love, it is likely that oxytocin contributes to the decreased stress levels and HPA axis activity seen in long-term relationships. How oxytocin and vasopressin influence HPA axis activity remains to be determined.

Taken together, these data show that there are clear alterations in HPA axis activity in romantic love. Unfortunately, the exact causes and consequences of these alterations are poorly understood. Stressors, altered vasopressin levels, and an increased likelihood to fall in love when experiencing a stressful period may all combine to cause the rise in HPA axis activity during early romantic love. Oxytocin may play a crucial role in reducing stress and HPA axis activity in long-term relationships.

Nerve growth factor

Nerve growth factor (NGF) is a neurotrophin involved in several processes, including survival, apoptosis, differentiation, and maturation of neurons (Freed, 1976). NGF is also known as an inflammatory mediator particularly associated with chronic airway diseases (Allen and Dawbarn, 2006). Furthermore, NGF plays a role in regulating certain behaviors associated with stress, including dominant/submissive behavior, and is important for maintaining hierarchical organization in male mice (Gioiosa et al., 2009). Hypothalamic NGF production is increased in stressful circumstances (Taglialatela et al., 1991). It induces HPA axis activity, and thus it plays a role in regulating the stress responses. Dysregulation of NGF levels has been linked to several psychiatric and neurodegenerative disorders, including depression, anxiety disorders, and Alzheimer's disease (Allen and Dawbarn, 2006; Gioiosa et al., 2009).

Recently, NGF was found to be elevated in the plasma of subjects who had recently fallen in love, but not in singles or subjects in long-term relationships (Emanuele et al., 2006). Moreover, NGF levels significantly correlated with the strength of feelings of romantic love, as measured by the Passionate Love Scale (Emanuele et al., 2006). Interestingly, during a second assessment 12–24 months after the start of the relationship, NGF levels had significantly decreased compared with the first assessment and were indistinguishable from NGF levels of singles and subjects in long-term relationships (Emanuele et al., 2006). These data indicate that NGF plays a role in the physiology of early-stage intense romantic love and attachment, but not in long-term relationships. It must be noticed, however, that NGF can also be a by-product of other physiological processes in the early stage of romantic love. Interestingly, *in vitro* studies have shown that NGF can upregulate the release of hypothalamic vasopressin (Scaccianoce et al., 1993). Thus, NGF might facilitate pair-bonding because of its effect on vasopressin levels.

Testosterone

Testosterone is a steroid hormone, which is secreted by the testes of males and the ovaries of females. This hormone exhibits several functions including the development of the male reproductive system and secondary sex characteristics (Mooradian et al., 1987; Eisenegger et al., 2011). However, testosterone is also involved in several aspects of social behavior, including social aggression (Strüüber et al., 2008), infant/mate defense (van Anders et al., 2011), and sexual intimacy (Wingfield et al., 1990). Furthermore, testosterone plays a role in romantic love and pair-bonding as indicated by reduced testosterone levels in men but elevated levels in women at the beginning of a new relationship (Marazziti and Canale, 2004). These differences fade after 12–24 months, suggesting that testosterone is involved in the early phase of romantic love. Furthermore, partnered men and women show decreased testosterone levels compared with singles (Burnham et al., 2003; van Anders and Watson, 2007), although sex differences have been observed in which the type of relationship influences the testosterone levels in women. As shown by van Anders and Watson (2007), women who are in a relationship with a man in the same city show lower levels of testosterone than women in a long-distance relationship (van Anders and Watson, 2007). This suggests that physical partner presence has an effect on testosterone (and perhaps other hormones) levels in women.

These observations suggest that testosterone is involved in the beginning of new relationships and that there are sex differences in the testosterone effects on romantic love. Furthermore, several factors have been elucidated that can influence the link between testosterone and romantic love. These factors also show sex differences with frequency of sexual intimacy playing a major role in females, whereas interest in more/new relationships can influence the link between testosterone and partnering in males (van Anders and Goldey, 2010). Although several involved factors are known, the exact mechanisms by

which testosterone can influence romantic love and partnering remain unclear.

BRAIN ACTIVITY IN LOVE

So far, few fMRI studies elucidating neural correlates of romantic love have been published (Bartels and Zeki, 2000, 2004; Fisher et al., 2005; Aron et al., 2005; Beauregard et al., 2009; Kim et al., 2009; Xu et al., 2011), and these studies are difficult to compare because they suffer from selection bias. However, some general conclusions can be drawn from these neuroimaging studies. Brain areas that show activation in romantic love are the medial insula, anterior cingulate cortex, hippocampus, striatum, nucleus accumbens, and hypothalamus (Zeki, 2007). These areas are important components of the brain reward system and all contain high concentrations of dopamine. Moreover, many regions are adjacent to, or in the case of the hypothalamus overlap with regions that show increased activity during sexual arousal (Brunetti et al., 2008; Walter et al., 2008; Hamann et al., 2004), making it likely that there are many interactions between these systems.

Parallel to activation of the aforementioned "core regions" in romantic love, several cortical areas, including the amygdala, frontal cortex, prefrontal cortex, temporal poles, and parietotemporal junction, are deactivated (Zeki, 2007). All these deactivated areas maintain close interactions with the activated core areas for romantic love. Cortical deactivations are usually right lateralized. Knowledge of the function of these cortical areas allows speculation about the role of cortical deactivations in human behavior in romantic love. The amygdala is associated with the experience of emotions, especially fear (De Carvalho et al., 2010; De la Mora et al., 2010; Shin and Liberzon, 2010; LeDoux, 2007), and its deactivation might reflect the lessening of fear that is experienced when being close to a loved one. Note that, as described before, oxytocin and vasopressin regulate amygdala activity in opposite manners, with oxytocin decreasing and vasopressin increasing amygdaloid output (Debiec, 2007). It seems to be a logical explanation that the decrease in amygdala activity in fMRI studies of romantic love implies that the effect of oxytocin is stronger than the effect of vasopressin, thus resulting in a decrease in amygdala activity. However, there could also be a sex bias because vasopressin is more important in male binding in prairie voles, whereas oxytocin is more important in female binding (Lim and Young, 2004; Wang et al., 1994; Winslow et al., 1998; Young et al., 2001; Insel and Hulihan, 1995). If the same sex differences also exist in humans, this could imply that changes of amygdala activity during romantic love are also gender specific. However, studies that have included both male and female subjects did not find a sex difference in amygdala activity (Zeki, 2007), and lessening of fear is reported in both males and females in long-term relationships (Esch and Stefano, 2005).

The frontal cortex is involved in the experience of negative emotions and judgment (Volz et al., 2006; Murray and Wise, 2010). The common observation that people who are in love are not able to honestly judge their lover's character, might thus be influenced by altered activity in this brain area. Other areas implicated in love are the prefrontal cortex, temporal poles, and parietotemporal junction. These areas are involved in mentalizing and Theory of Mind (evaluating other people's feelings and intentions) (Zeki, 2007).

Several studies have described the similarities and differences in brain activity between maternal and romantic love (Bartels and Zeki, 2004; Beauregard et al., 2009; Noriuchi et al., 2008). It turns out that there is great overlap in brain activity between both kinds of love. Maternal as well as romantic love activates the dopamine reward system, and also the pattern of brain deactivations is largely similar (Zeki, 2007). These observations support the hypothesis that the adult attachment system evolved from the infant–caregiver attachment system (Zeki, 2007). However, there are also some differences. One interesting difference involves the hypothalamus, which is activated in both romantic love (Bartels and Zeki, 2004) and sexual arousal (Fisher et al., 2006), but not in maternal love (Bartels and Zeki, 2004). Thus activity in the hypothalamus might constitute the sexual aspect of romantic relationships, which is usually absent in infant–caregiver relationships. Another difference is that in maternal love strong activation was found in areas specific for face recognition and facial expressions. Zeki (2007) suggested that the strong activation of these areas in maternal, but not in romantic love can be attributed to the evolutionary necessity for mothers to read their children's facial expressions, to assure their well-being.

It is likely that also other kinds of love, including close friendships and family bonds, make use of the same neuronal network that is active in maternal and romantic love. However, no studies have investigated brain activity in these kinds of love so far. Few fMRI studies have investigated brain circuits involved in love, but without doubt more such studies will follow in the next couple of years. These studies may further explore the similarities and differences between different kinds of love, as well as changes during the evolvement of a relationship.

GENDER DIFFERENCES IN LOVE

Many psychologists have studied gender differences in love relationships. Although these differences tend to be small, there are some indications that women value companionship slightly more than men and are more likely to disclose their feelings to their partner, whereas men surprisingly score slightly higher on romantic ideologies (O'Leary et al., 2006). It is important, however, to keep in mind that gender differences in love are also highly dependent on culture.

Despite the variety of psychological literature on gender differences in love, there have been surprisingly few neurobiological studies investigating this topic. As functional neuroimaging is increasingly used to study emotions, including love, more studies in this area can be

expected in the next few years. The few studies that have been performed however did find some gender differences (Fisher et al., 2006). While women showed increased activity in regions associated with attention, emotion, and memory, men showed increased activity in areas associated with viewing beautiful faces and the integration of visual stimuli. Fisher et al. (2006) suggested that these differences are caused by a greater importance for men to pay attention to signals of youth and health in women, thus enabling them to choose those women that are fit for childbirth, whereas women on the other hand have to remember male status and male accomplishment in the past to be able to choose those men that are able to provide enough resources for their children. Indeed, psychological literature shows that men are more attracted to beauty, whereas women pay more attention to male status (Buss et al., 1990).

There is also a biological reason why gender differences in love are likely to occur. The effects of oxytocin on attachment and sexual behavior are estrogen dependent (Keverne and Kendrick, 1994; Fahrbach et al., 1984) and gender specific. There are studies showing that in prairie voles, oxytocin is more important for attachment in females, whereas vasopressin plays a more important role in males (Lim and Young, 2004; Wang et al., 1994; Winslow et al., 1998; Young et al., 2001; Insel and Hulihan, 1995). As attachment seems to be regulated in a slightly different way in both sexes, it is likely that there will also be functional differences. However, what these differences are and whether the same differences occur in humans needs to be further determined. Receptor distribution is also different between male and female prairie voles (Insel and Shapiro, 1992; Young et al., 1998) and some receptors might be sexually dimorphic, further supporting the theory that there are gender differences in love and attachment (Wang and Aragona, 2004). It has also been demonstrated that male and female rodents respond differently to stress (Ter Horst et al., 2009; Lin et al., 2009). While female stress responses and brain activity are positively correlated with social housing, they are negatively correlated in males (Westenbroek et al., 2005). Based on these findings we hypothesized that in the male and female brain different strategies are used to cope with stressful situations, including early stages of romantic love (Ter Horst et al., 2009). In later stages of a romantic love affair, when stress levels are normalizing, these sex differences may be less explicit.

Although there are definitely indications that neurobiological systems in love are partly gender specific, more research is needed to define the exact gender differences and how they influence human behavior and attitudes towards love.

THE COURSE OF A RELATIONSHIP

It is obvious that romantic relationships evolve over time. According to the Triangular Theory of Love (Sternberg, 2007), there are three components of love: passion, intimacy, and commitment. These components differ among different kinds of relationships, but also evolve over time within a relationship. Psychologists have defined three different phases in romantic relationships: “Being in Love,” “Passional Love,” and “Companionate love” (Garcia, 1998). Each phase has its own characteristics, as well as neurobiological backgrounds. We will discuss each phase in brief. Although not technically a phase in a relationship, we will also discuss the breakup of a relationship and the grieving period afterward. It is important to keep in mind that every relationship is different and that individual relationships may differ from the general course presented here.

Phase 1: Being in love

“Being in love” is the first phase in a relationship. This phase is characterized by high passion, a rapid rise in intimacy, and increased commitment (Garcia, 1998). This phase lasts relatively short, usually around half a year. Love during this phase has the character of excitation and stress (Berscheid, 2010; Starka, 2007). Stress is caused by insecurity and can lead to mood changes. Although cortisol levels are elevated during this phase, follicle stimulating hormone (FSH) and testosterone levels are downregulated. Both changes are typical for stressful situations (Marazziti and Canale, 2004). As described before, the early phase is also characterized by high NGF (Emanuele et al., 2006) and low serotonin levels (Marazziti et al., 1999).

Phase 2: Passional love

After several months to a year (Marazziti et al., 1999; Marazziti and Canale, 2004; Garcia, 1998; Starka, 2007), the initial phase of euphoria, excitation, and stress evolves into a phase of “passional love” (Garcia, 1998), which is dominated by feelings of safety, calm, and balance (Starka, 2007). Levels of several neuroendocrine factors found to be abnormal in early romantic love, including NGF (Emanuele et al., 2006), platelet serotonin transporter (Marazziti et al., 1999), and abnormalities in the HPA-axis (Marazziti and Canale, 2004), have by this time returned to normal. In this second phase, passion remains high, whereas intimacy and commitment continue to increase steadily (Garcia, 1998). Stress is decreased, which may result in several health benefits (Esch and Stefano, 2005). Furthermore, oxytocin and vasopressin are believed to be the major factors during this phase because they are involved in the formation of strong pair-bonds between the couple (Starka, 2007).

Phase 3: Companionate love

The phase of passional love usually lasts several years before evolving into companionate love. This phase is characterized by a decrease in passion, whereas intimacy and commitment remain high (Garcia, 1998). Actually, the love relationship in this phase is quite similar to friendships. Again, oxytocin and vasopressin are thought to be the dominant hormones, reinstating and maintaining pair-bonds between the couple (Starka, 2007).

Not all relationships eventually evolve into companionate love. Many relationships end during earlier phases. The earlier described “4 years itch” (Fisher, 1992) coincides with the end of the passional love phase, indicating that the transition from passional love to companionate love is a particularly fragile period in a relationship. When intimacy is low, commitment may be all that is left after passion has declined, a kind of love that is referred to as “empty love” (Sternberg, 2007). Many couples will break up in this situation, contributing to the “four years itch” effect, but if commitment to the relationship is strong enough the couple might stay together. On the other hand, some couples claim to be still passionately in love with each other after 20 years of marriage, indicating that some relationships may never evolve into companionate love, but instead remain in earlier phases. It is yet unclear what factors cause a relationship to follow a particular course.

Breakup of a relationship

Unfortunately most relationships do not last forever. Breaking up a relationship is often, although not always, experienced as very stressful (Field et al., 2009), and increases in stress hormones are commonly seen. So far three studies have investigated the patterns of brain activity after a romantic breakup (Fisher et al., 2010; Najib et al., 2004; Stoessel et al., 2011). Fisher et al. (2010) found an increased activity in the ventral tegmental area, ventral striatum, pallidum, and putamen in individuals experiencing a romantic relationship breakup. These areas are part of the reward system in the brain and are indicated in choices for uncertain rewards and delayed responses (Fisher et al., 2006; Cardinal and Howes, 2005). Indeed, uncertainty about the future is a common feeling after a romantic breakup. Next to this, parts of the orbitofrontal cortex were activated, which is associated with Theory of Mind and implementing appropriate adjustments in behavior, but have also been found to be activated in obsessive-compulsive behaviors and in anger control (Fisher et al., 2006). In contrast, Najib et al. (2004) found deactivation of most of these areas. However, the individuals studied by Najib et al. (2004) were in a later stage after breaking up, and acceptance was more common in this group than in the group investigated by Fisher et al. The differences found most likely reflect changes in brain mechanisms over time as one learns to accept and deal with the romantic breakup. Stoessel et al. (2011) performed the most recent fMRI study on relationship breakups. Results showed that rejected individuals had decreased activity in a brain network, which has been described as being involved in major depression. Furthermore, subjects were experiencing clinical depressive symptoms based on the Beck Depression Inventory, suggesting that there is a close relationship between grief and depression and that the grieving period following a romantic relationship breakup might be a major risk factor for clinical depression.

For future research on romantic relationship breakups, it would be interesting to study changes in brain activity over time in individuals who recently ended a relationship. Here, gender differences may appear as it is demonstrated that male and female rodents cope differently with stress (Ter Horst et al., 2009), woman are more susceptible to stress-related diseases (Piccinelli and Wilkinson, 2000), males are prone to develop substance abuse (Wang et al., 2009), and a lack of social support may be a factor that makes it more difficult for women to cope with stress of a relationship breakup (Westenbroek et al., 2005; Kendler et al., 2005).

HUMAN MONOGAMY: TRUTH OR MYTH?

Little is known about the factors that influence the course of a relationship and may predict its ending. What is known is that most of the relationships break up sooner or later. A simple look at divorce rates shows that about one-third of all marriages may end in divorce. In early romantic relationships, breakup percentages are thought to be even higher (Kalmijn, 2007). Furthermore, adultery is a common phenomenon in our society, and in many societies polygamy is commonly accepted (Blow and Hartnett, 2005). These data raise the question whether humans are really monogamous.

There are several indications for human nonmonogamy. First of all, psychological research has shown that marital satisfaction is inversely correlated with marriage duration (Berscheid, 2010), and many marriages end up in divorces (Kalmijn, 2007). Second, there are studies that indicate that there are fragile moments in a relationship at which breakup is more likely to occur. The “four years itch” is an example of such a moment (Fisher, 1992). Both observations indicate that there are mechanisms that lead to relationship breakups, suggesting that humans are not naturally inclined to form life-long attachments. Furthermore, comparing humans with other species showed that on several points, including male and female size, sexual maturation in females, and predominance of violence in males, humans are more similar to nonmonogamous species than to monogamous species (Barash and Lipton, 2002).

Although the previous data suggest that humans are not monogamous, humans display too many qualities of social monogamy, including enduring pair-bonds and cooperation in raising offspring, to conclude that humans are completely nonmonogamous. In fact, it is possible that humans, just like other monogamous species, are evolutionary programmed to be serial monogamous, showing high levels of social monogamy without being sexual monogamous. In this context, it would be interesting to study human genetic polymorphisms involved in monogamy. Attempts have already been made, studying polymorphisms of the vasopressin (Solomon et al., 2009; Mabry et al., 2011) and oxytocin genes (Liao et al., 1996) and of the gene for the dopamine D2 receptor (Emanuele et al., 2007), but no study so far has convincingly linked any polymorphism to a higher or lower level of monogamy. Also, studies on the effects of individual biological differences on monogamous behavior could provide more knowledge about how exactly differences in monogamous behavior are regulated.

In conclusion, the question whether or not humans are monogamous is difficult to answer. Humans exhibit clear traits of social monogamy, but it seems unlikely that humans are naturally inclined to be sexually monogamous, and human pair-bonds seem not to be made for eternity. However, human monogamy is still a sensitive topic and many people would not share this opinion. A complicating factor is that culture also plays an important role in human sexual behavior, and it is difficult to separate this cultural effect from human nature.

CONCLUSION

Although there are a wide variety of psychological studies investigating the phenomenon of romantic love, neurobiologists have only recently started to show an interest in romantic love as a topic of research. The few fMRI studies in human subjects that have been performed so far show contradicting results and may suffer from selection bias. Studies using prairie voles give some insights in general attachment mechanisms, but it is questionable whether these results can actually be extrapolated to humans. At this moment there is a lack of temporal studies investigating brain activity as well as endocrine factors over the course of a relationship. We would therefore want to argue for the setup of a large longitudinal study, including a large number of subjects at the beginning of (or possibly before the start of) a new relationship. In these subjects, regular fMRIs should be performed to follow changes in brain activity over time, preferably in combination with gene profiling of the participants. Also, blood samples should be taken regularly to follow the levels of certain endocrine factors over time. These data could be correlated to psychological data from interviews and questionnaires. Such a study would provide valuable insights into temporal changes in brain activity and levels of endocrine factors and could moreover provide more information about gender differences in love. Although such a longitudinal study is difficult to set up, human romantic love is a topic of continuing interest and more studies into its neurobiological correlates, leading to new insights, can be expected in the next few years.

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