

Masterthesis

Master Neuroscience and Cognition, CN track

The overlap between romantic love and addiction

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Abstract:

Many parallels can be drawn between the behaviour of those who are in love and those who are addicted. Their behavior is characterized by a preoccupation with obtaining the reward, and spending time with the target of the preoccupation, as well as a lack of interest in any other activities. Both love and addiction can be divided in an initial formation stage, a maintenance stage and if applicable a disruption stage. The formation of both love and addiction critically relies on changes in the mesolimbic pathway. For love also activity in the oxytocin/vasopressin system is necessary, this system is tightly coupled to the natural reward system. The behavior is maintained by the increase incentive salience of the drug or the partner, as well by the aversive effects of withdrawal or separation. When a pair-bond is disrupted or drug consumption is discontinued, a depression in activity of the mesolimbic system is observed. Although the changes in the natural reward system underlying love and addiction overlap to some degree, there are also marked divergencies. In addition, there are also pronounced behavioral differences between love and addiction. Importantly, love is not a compulsive behavior, but it is guided by normal hedonic sensations and motivation. It can therefore not be concluded that love in general is an addiction. On the other hand, in exceptional cases, maladaptive, perhaps compulsive forms of love occur, that may be akin to addiction.

Table of content

1. Introduction

- 1.1 Similarity in “symptoms” 4
- 1.2 Hypothesis: Love is an addiction. 4

2. Brain areas & endocrine factors in love

- 2.1 Definitions of types/stages of love 6
- 2.2 Animals and humans: pair-bonds versus love 7
- 2.3 Animals: monogamous and non-monogamous species 8
- 2.4 The formation of a pair-bond and falling in love 8
- 2.5 The maintenance of a pair-bond and staying in love 14
- 2.6 Pair-bond disruption and relationship dissolutions 18

3. Brain areas & endocrine factors in addiction

- 3.1 Drug addictions 21
- 3.2 Behavioral addictions 23
- 3.3 Definition of addiction 23
- 3.4 Human and animal studies 24
- 3.5 Development of addiction 24
- 3.6 The maintenance of addiction 28
- 3.7 Abstinence and relapse 30

4. Discussion

- 4.1 Overlaps and differences between love and addiction 32
 - 4.1.1 Incentive sensitization 33
 - 4.1.2 Allostasis in the dopaminergic system 35
 - 4.1.3 Stress and corticotrophin-releasing factor 36
 - 4.1.4 Changes in the prefrontal cortex 37
- 4.2 The interaction between love and addiction 37
- 4.3 Is love an addiction? 38
- 4.4 Possible maladaptive forms of love as love addiction 39
- 4.5 Future research 41
- 4.6 Conclusions 42

5. References

43

1. Introduction

Romantic love is one of the most fundamental experiences in human life. The scientific interest in what exactly love is has increased over the past decades. Romantic love has often been described as an addiction in music, art and literature. There are abundant examples of stories of romantic love that involve great sacrifices, such as alienating their families just be with their beloved. Similar sacrifices are made by addicts to obtain and use their drugs. Due to the similarities in behavior of addicts, those hopelessly in love, and the heartbroken, a number of psychologists also view love as an addiction (e.g., Griffin-Shelly, 1991; Halpern, 1982; Shaef, 1989).

1.1 Similarity in “symptoms”

The first step in determining whether love is an addiction is the comparison of the similarity in symptoms. In table 1 the DSM-IV criteria for substance dependence and their analogs in love are described. As can be seen in the table, the symptoms of addiction and romantic love have much in common, the early phase is filled with euphoria, anticipation of the next “high”, and continuous preoccupation with the beloved or the drug. All sensations during the encounters are coupled to the beloved, the sounds, the smells, but also it seems like there is a complete loss of the surroundings, as if the rest of the world does not exist. After a while the euphoric sensations wane and are replaced by less intense feelings of calm and contentment with each encounter. Although when separated a strong feeling of missing and desire is present, which is relieved by the next interaction. Furthermore drug use is continued even when someone wants to quit, which similarly can happen in on-again, off-again relationships. And when it all finally stops feelings of desperations and grief emerge.

1.2 Hypothesis: Love is an addiction

So parallels between the symptoms of love and addiction can be drawn and several professionals consider love to be an addiction, it is the question how valid this assumption is. In order to answer this question the following hypothesis is the topic of this thesis: *Love is an addiction. If this is the case the same neural mechanisms and adaptations should be involved in both love and (behavioral) addictions.*

In the following chapters the validity of this claim is investigated by first discussing the neural systems involved in love (Chapter 2), and addiction (Chapter 3). In the discussion (Chapter 4) the answer to the hypothesis will be provided.

Table 1: The DSM-IV criteria for the diagnosis of substance dependence and their analogs in love. (Copied from Burkett & Young, 2012)

Substance dependence criteria	Analog in social attachment
Great deal of time spent in activities necessary to obtain, use, or recover from use	Dating; parenting
Substance is taken in larger amounts or over a longer period than intended	Sensation of "time flying" when with the partner
Important social, occupational, or recreational activities are given up or reduced	Loss of time with friends
Tolerance	Transition from early euphoria to contentment
Withdrawal	Grief (from loss); separation anxiety when apart
Unsuccessful efforts to cut down or control use	Sensation of not being able to stay away from the partner; failed attempt(s) to break up
Continued use despite knowledge of a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by use	Physically or emotionally abusive relationships; staying with someone who "isn't right for you"
Related behaviors	
Stress-induced reinstatement	Consolation-seeking
Dependence-induced increase in drug consumption	Increase in time spent with the romantic partner as the relationship grows
Withdrawal-induced anhedonia and depression	Anhedonia and depression induced by loss or separation

2. Brain areas & endocrine factors in love

2.1 Definitions of types/stages of love

Romantic love is clearly one of the most fundamental aspects of human life. It is seen as a complex and intense sentiment towards another individual (Bartels & Zeki, 2000). Love is identified across all cultures, and two different types are consistently identified, romantic/passionate love (being in love) and compassionate love (loving) (Jankowiak & Fischer, 1992). The two types of love are considered valid concepts, regardless of gender, age or culture (Hatfield & Rapson, 1996). How these two types of love differ, change from passion to compassion, and what mechanisms underlie these changes has been of scientific interest for the last couple of decades. It is considered that love relies on three discrete but interrelated motivation systems in the brain, for lust, attraction and attachment (Fisher, 1998; Fisher et al., 2002; 2006). In this thesis the changes the brain undergoes when one falls in love, changes from passionate love to compassionate love, and the impact of a relationship dissolution will be discussed. Before these changes are discussed, the types of love need to be defined.

Passionate/romantic love is seen as a motivational state (Acevedo et al., 2012; Aron et al., 2005; Ortigue et al., 2007) or a powerful complex emotion (Burkett & Young, 2012) which functions to establish a selective bond with a preferred individual (Fisher et al., 2002). This selective bond arises as passionate love is coupled with the inability to feel passion towards more than one person (Berscheid & Meyers, 1996).

The first phase of passionate love, is falling in love This very arousing but also stressful phase is thought to last about six months (García, 1998; Marazziti & Canale, 2004). Falling in love is characterized by intense emotional responses, such as euphoria, intense focused attention on the preferred individual, obsessive thinking about him or her, emotional dependency on and craving for emotional union with the beloved, as well as increased energy when together (Aron et al., 2005). Some of these characteristics during this phase of love are very similar to the symptoms of obsessive compulsive disorder (OCD). For example anxiety, stress and the obtrusive thoughts are prominent in OCD and falling in love (Marazziti et al., 1999). After a few months the feelings of stress decrease and are replaced by feelings of calm, safety and balance (Stárka, 2007). During this phase passion between lovers remains high, and intimacy and commitment rise (García). This phase usually lasts several years, which gradually changes into compassionate love (De Boer et al., 2012). In general it seems

to take about two years for enduring attachment bonds to be established (Hazan & Zeifman, 1994).

Companionate love: After about four years passionate love has changed into compassionate love (García, 1988). During this time passion gradually decreases while intimacy and commitment remain high (García). Compassionate love resembles more of a deep friendship with easy companionship and sharing of common interests, but not necessarily involving intensity, sexual desire, or attraction which marks the passionate love phase (Acevedo et al., 2012). The transition period from passionate love to compassionate love is a very fragile phase for a relationship. This is illustrated by a major peak in relationship dissolutions that happen after being together for four years (Fisher, 1992). Although it should be noted in some very long relationship passionate love can still remain very high (Acevedo et al.). Thus the change into compassionate love does not need to happen in all relationships.

2.2 Animals and humans: Pair-bonds versus love

In order to gain insight into the neurobiology underlying love, animal models provide an interesting opportunity. Unfortunately it is hard to operationalize love in animals, but for the main function of love it can be done, the formation of an enduring selective pair-bond with a preferred individual. Across species such selective pair-bonds are observed, although only in 3-5% of the mammals (Kleiman, 1977).

The main behavioral features of a pair-bond are selective contact, affiliative behavior and exclusive mating between the two bonded individuals (Young et al., 2011a), although in some cases extra-pair copulations are observed (Wolff et al., 2002). These adult pair-bonds seem to have evolved from mother-child bonding to further increase offspring survival by providing bi-parental care (Fisher, 1998). This precursor of mother-infant bonding is present in most mammalian species (Insel & Young, 2001).

The most studied animal model of adult attachment is the prairie vole (*Microtus ochrogaster*). In the wild the voles form enduring pair-bonds, and both parents provide care for their young (Young et al., 2011a). When one of the voles dies, the remaining vole rarely takes on a new partner (Getz & Carter, 1996), importantly in the laboratory these behaviors persist. A pair-bond is formed if two prairie voles mate and cohabite for 24 hours, while no bond is formed after only six hours of cohabitation and mating (Williams et al., 1992; Winslow et al., 1993). If the pair is separated after forming partner preference, the preference declines after eight days and is absent after ten days of separation (De Vries, unpublished

data in Carter et al., 1995). In experiments the pair-bond is tested by the partner preference test and selective aggression towards others than the mate.

2.3 Animals: monogamous and non-monogamous species

As stated before, adult attachment seems to have evolved from maternal attachment, to increase offspring survival. Evidence for this claim is that most species that form pair-bonds show bi-parental care (Fisher, 1998). The prairie voles provide an interesting model for monogamous pair-bonds because they can be compared to closely related vole species, the montane and the meadow vole (Lim et al., 2004). These voles are non-monogamous and do not display bi-parental care. Prairie voles have higher receptor densities of the two closely related “social” neuropeptides Oxytocin (OT) and Vasopressin (AVP), than the non-monogamous vole species. OT and AVP are exclusively found in mammals (Insel, 2000) and are necessary for a variety of social behaviors, which underlie the formation of a pair-bond. For instance OT and AVP work in concert in to promote approach behavior, social information processing, recognition and long-term social memories (Lim & Young, 2006). Also OT is necessary for the formation of mother-infant bonds (Lim & Young). Prairie voles have oxytocin receptors (OTR) in the caudate putamen (CP) and the Nucleus Accumbens (NA) (Insel & Shapiro, 1992), and vasopressin receptors (V1aR) in the ventral pallidum (VP), medial amygdala and the mediodorsal thalamus (Insel et al., 1994), while these receptors are not present at these sites in the non-monogamous voles. Interestingly when V1aR in the VP of the male meadow voles is overexpressed, they form partner preferences similar to the prairie vole (Lim et al.). Although in female meadow voles the overexpression of OTR in the NA does not induces the formation of a partner preference (Ross et al., 2009). The formation of a partner preference in the male meadow vole is also critically dependent on dopamine (DA) transmission (Lim et al.). The specific roles of OT, AVP and DA in the formation of pair-bonds will be further discussed in the following section.

2.4 The formation of a pair-bond and falling in love

In prairie voles the formation of a pair-bond is the result of positive reinforcement learning, which relies on the activation of DA, AVP and OT receptors during sex (Young et al., 2005), see figure 1 for an overview of the brain areas involved. When a partner preference is formed changes in the expression of (some) these receptors are observed. This naturally occurring brain plasticity is thought to inhibit the formation of other bonds and also to maintain the existing bond.

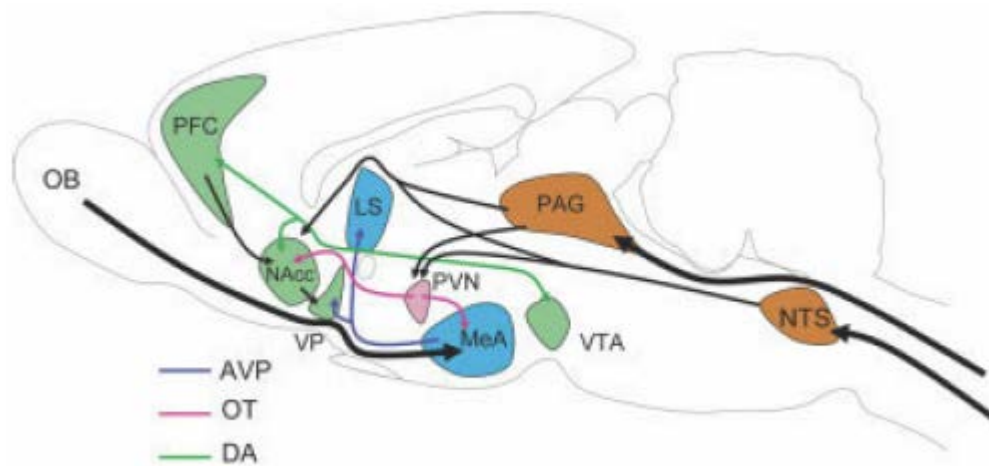


Figure 1: Proposed anatomical circuitry of social bonding in prairie voles. Somatosensory input from the genitalia is transmitted by the tractus solitarius (NTS) and midbrain periaqueductal gray (PAG). This information is projected to the NA and the paraventricular nucleus (PVN). Olfactory information of the partner is conveyed to the medial amygdala (MeA) which facilitates recognition, in turn the MeA transmits to the VP and LS for the formation of memories. Furthermore activation of the VTA during mating results in DA release in the PFC and NA (Copied from Young et al., 2005).

The partner preference formation relies on the co-activation of AVP/OT receptors and a subtype of the dopamine receptors, the D2R in the mesolimbic areas (Aragona & Wang, 2009; Liu & Wang, 2003). For instance infusing agonists for these receptors facilitates the formation of partner preference in both males and females without mating and/or during short time cohabitation (Aragona et al., 2006; Cho et al., 1999; Gingrich et al., 2000; Williams et al., 1992; Winslow et al., 1993). On the other hand blocking either the transmission of D2R, OTR, or V1aR by an antagonist blocks partner preference formation during extensive cohabitation with mating (Aragona et al., 2003; 2006; Cho et al., 1999; Liu et al., 2001; Liu & Wang, 2003; Winslow et al., 1993; Young et al., 2001). But once the partner preference is formed D2R activation is not necessary for the subsequent expression of the behavior. For instance the administration of a D2R antagonist in an established breeder pair does not disrupt the display of the partner preference (Wang et al., 1999).

Critically for the formation of the pair-bond is the interaction of AVP/OT and DA. For instance infusing an OTR antagonist in the NA of female prairie voles blocks partner preference formation induced by D2R activation (Liu & Wang, 2003). And conversely blocking D2R in the NA prohibits partner preference induced by OT. In males these

experiments are not yet done but a similar interaction between the AVP system and D2R in the NA-VP circuitry is expected.

The involvement of the reward system is hypothesized to assign salience to the partner, and subsequently increase the motivation to interact with the partner (Young et al., 2011a). As stated before a pair-bond is formed after 24 hours cohabitation and mating, during mating dopamine (DA) is released in the NA of both male and female prairie voles (Aragona et al., 2003; Gingrich et al., 2000). The pair-bonding is the result of conditioned reward learning due to the reinforcing properties of sex (US) coupled with the smell of the partner (CS) (Insel, 2003; Insel & Young, 2001). During mating also the OT and AVP system are activated. Vaginal simulation releases OT after birth, and is also thought to happen during mating (Lim & Young, 2006). At least there is indirect evidence of OT release during mating, inferred by antagonist infusions, and of AVP release in the VP during ejaculation (Young et al., 2005).

In non-monogamous species mating also results in DA release in the NA (Becker et al., 2001; Pfaus et al., 1990), but V1aR and OTR are not expressed in the mesolimbic pathway of non-monogamous species (Lim et al., 2004). This could mean that social recognition is not activated in these species during mating and thereby fail to associate the rewarding effects of mating with the specific partner. Alternatively the very primitive discriminative social memory of many species could also be responsible for the absence of pair-bonding. For instance rats can only discriminate between colony and non-colony conspecifics and seem to only form temporary social memories (Wacker & Ludwig, 2012). Interestingly in male rats a conditioned partner preference can be induced after mating if the female is scented with a non-social scent (Pfaus et al., 2001).

The other predominant DA receptor type, D1R, has an opposing role in the formation of a pair-bond. The activation of D1R in the NA blocks partner preference formation (in males), either induced by mating or D2R activation (Aragona et al., 2006). After two weeks of cohabitation with the partner D1R in the NA is up-regulated. This up-regulation is not the direct result of partner preference formation because 24 hours of cohabitation with mating does not result in an increase in D1R binding in the NA. The increase in D1R after extended cohabitation contributes to the maintenance of the pair-bond; the details will be further discussed in the section on pair-bond maintenance.

In contrast to prairie voles, falling in love in humans is a far more complex phenomenon than the coupling the rewarding effect of sex with the specific partner. But certainly includes reinforcement learning, and many of the same brain areas that are involved

in pair-bonding and falling in love. For instance imaging studies have consistently found activation in the areas of the reward system when viewing a picture of the partner (see figure 2 for an overview). For instance, Aron et al. (2005) scanned men and women who had recently fallen in and found activation in the VTA and the CN. These are DA rich areas which are implicated in the motivation to acquire a reward. This effect is also found on an implicit level, subliminally presenting the name of the partner versus that of a friend or stranger activated the same areas (Origue et al., 2007). These areas are adjacent to and overlapping with areas that are activated during sexual arousal and intercourse, implicating interactions between the two systems (De Boer et al., 2012). Therefore it is not unlikely that there is a bi-directional influence of love and sex on each-other as both activate areas rich in receptors for DA, OT and AVP. Although it should be noted that love can certainly happen in the absence of sex, and has, at least for serotonin functioning, the same impact on the brain (Marazitti et al., 1999).

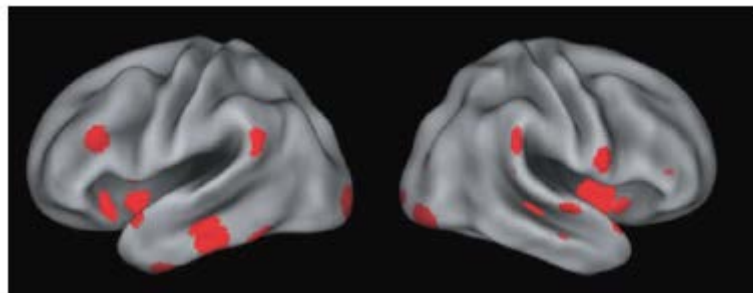


Figure 2. fMRI brain activation during romantic love, data collapsed from several studies imaging romantic love (N = 70; 57 females and 13 males) (Copied from Ortigue et al., 2010)

In another study Langeslag et al. (in press) implicated that the activity in the dorsal striatum reflects prior reinforcement learning related to the partner. In the study the picture of the partner and a friend were used both as targets and distracters. In contrast to the picture of the friend, increased dorsal striatal activation was found when the partner was the target, while it was decreased during the distracter condition. Especially convincing is that the magnitude of the activation in the dorsal striatum was correlated with the duration of love. Furthermore Aron et al. (2005) also found activation in the septum which correlated with self-reported passionate love, which is an area that is rewarding during self-stimulation (Olds & Milner, 1954). Importantly the LS is also essential in male prairie voles for partner preference formation by the activation of V1aR and probably D2R (Liu et al., 2001).

It is striking that those who have recently fallen in love (1-7 months) have greater

activation in the retrosplenial cortex than the participants who were in love for eight months or longer (Aron et al., 2005). In this area AVP binding is higher in monogamous species than in non-monogamous species (Ophir et al., 2008b). And interestingly in male prairie voles V1aR density in the retrosplenial cortex correlates with the amount of mate guarding and sexual fidelity (Phelps & Ophir, in press in Phelps et al., 2010). This behavior is probably the result of maintaining close spatial proximity with the partner. This is because the retrosplenial cortex is an area implicated in spatial memory and the V1aR density is negatively correlated with home range distance (Phelps et al.). The greater activation during (uncertain) earlier phase of the relationship could reflect an increased level of proximity seeking. It is intriguing that the activation this area is lowered the same timeframe as a relationship is marked by low anxiety and high feelings of safety and calm (García, 1988). Unfortunately it was not investigated if the activity was related with feelings of anxiety over the relationship or consolidation seeking with the partner, so this claim is speculative.

Besides the imaging studies, changes in hormone levels have been found in those who have fallen in love. For instance OT plasma levels were elevated in men and women who recently had fallen in love compared to singles (Schneidermann et al., 2012). These levels were still elevated during follow-up and were correlated with relationship duration and positive social interaction between the partners. Unfortunately, OT levels were not measured before falling in love, so it is the question whether these OT levels reflect trait or state love. This study indicates that OT is involved in social bonding in humans. Although, not unsurprising, the relationship between OT and partner preference formation in humans is not as straightforward as in prairie voles. The only study that investigated the effect of intranasal OT administration in humans on (romantic) partner preference formation revealed no differences between the OT and placebo condition (Liu et al., 2013). It should be noted that this study has some limitations, for instance half of the participants were already in a committed relationship, and it was not examined whether OT administration had different effects with relationship status. Also the romantic context was imposed the day after the administration, which might have its impact on the findings (Bartz et al., 2011).

That falling in love is an arousing and sometimes even stressful experience, is reflected by the higher levels of cortisol and lower levels of FSH and testosterone in men who recently have fallen in love compared to singles (Marazziti & Canale, 2004). For women those levels were reversed with relationship status, except for cortisol. These levels are typical for stressful situations and reflect increases in hypothalamic-pituitary-adrenal (HPA) axis activity (De Boer et al., 2012). The role of stress might be to overcome neophobia

(Marazziti & Canale), or to facilitate pair-bonding (De Vries et al., 1995; 1996). But it is also possible that the stress is caused by the uncertainty of this phase could be related to the fear of losing the partner and/or the obsession during falling in love. Interestingly pair-bonding in prairie voles alters corticotropin-releasing factor (CRF) tone, which is a precursor for cortisol, in the bed nucleus of stria terminal (BNST). This alteration might prime the brain to respond quickly to social stress (Bosch et al., 2009). Similarly in humans it is thought that as the relationship progresses the partner starts to function as a stress buffer (Sbarra & Hazan, 2008) Possibly by the influence of OT and AVP on HPA axis activity (Gilleies et al., 1982; River & Vale, 1983; Legros, 2001). This effect should be the result of a conditioning of the stress buffering effect of the partner, and that subsequent (prolonged) separation from the partner should result in stress. It is considered that the aversion for separation helps maintain the pair-bond, this will be further discussed in the section on pair-bond maintenance.

Besides being a side effect of stress, the changes in testosterone might have gender specific functions. For females the increases in testosterone could function to increase the sex drive and for males to decrease interest in other women (Van Anders & Goldey, 2010). Alternatively the testosterone levels could just reflect an increase in the sex-drive in woman. It has been found that testosterone levels correlate with sexual desire in woman, while no relation between testosterone levels and sexual desire has been found in men (Van Anders, 2012).

Furthermore serotonin levels are also altered in during falling in love and are indistinguishable from those who are diagnosed with OCD (Marazziti et al., 1999). These changes are related to a decreased functionality in the serotonin transporter, which might cause the similarity of behavior during early stage love and OCD symptoms. During the follow-up, a year later, the serotonin levels had returned to normal and also the obsessive thought were gone. There is an indication that there are sex differences in the plasma and serum levels of serotonin of men and women who recently had fallen in love compared to those who are not in love. Langeslag et al., (2012) found that in men who were in love serotonin levels were lowered, while in women the level was elevated. This finding in women was unexpected and unfortunately the earlier studies did not consider gender differences. Furthermore only peripheral levels could be considered, and it is the question to what extent they reflect central levels. Serotonin has a sophisticated regulatory role of the DA system (Alex & Pehek, 2007; Dayan & Huys, 2009) and is implicated in all three aspects of reward, wanting, liking and learning (Kransz et al., 2010). Unfortunately little is known of the influence of serotonin in pair-bonding in animals, and whether serotonin levels are altered

during partner preference formation, although one study showed that the administration of a Selective Serotonin reuptake inhibitor (SSRI) decreased aggressive behavior of male prairie voles towards intruders (Villalba et al., 1997). But it cannot be said for certain that this effect is due to altered serotonergic activity, because this SSRI also influences the AVP system which, as will be discussed in the next section, regulates mate guarding related aggression (Winslow et al., 1993).

In summary falling in love is related to DA activity in the mesolimbic pathway of both animals and humans. There is evidence that OT and AVP activity is needed for the formation in the prairie voles, and is also implicated in humans. Falling in love is also a stressful experience which could be the result of the uncertainty of falling in love, but subsequently be responsible for the maintenance of the bond. In humans also serotonergic activity is altered and is probably related to the obsession during this phase. All these changes when falling in love function to establish a bond, in the next section the mechanism of maintaining this bond will be discussed.

2.5 The maintenance of a pair-bond and staying in love

With extended pair-bonding prairie voles become more affiliative towards each-other (Aragona et al., 2006). But affiliative behavior alone is not sufficient to maintain the pair-bond, aggressively rejecting intruders is essential. The aggression serves both to protect the pups and prevent the partner from mating with another conspecific, especially because prairie voles are only socially monogamous, not sexually (Carter et al., 1995; Ophir et al., 2008a). It is interesting that the aggression is highest towards same sex strangers for both males and females, while towards opposite sex intruders the aggression is more modest and variable (Aragona et al., 2006; Wang et al., 1997).

In males the aggressive behavior is only developed if the female becomes pregnant (Resendez et al., 2012). In contrast the aggression by female prairie voles is not related to pregnancy status (Resendez et al.), and could be related to the level of male investment, because the female aggressiveness correlates with duration of cohabitation (Bowler et al., 2012).

As discussed in the previous section the extended cohabitation with a partner increases the D1R density, but not D2R, in the NA (Aragona et al., 2003). This increase in D1R density coincides with the time that male prairie voles also start to become very aggressive towards intruding females, even when their partner is removed (Aragona et al., 2006; Gobrogge et al., 2007). And the activation of D1R is responsible for the expression of

selective aggression towards intruders (Aragona et al., 2006). Another function of the up-regulation of D1R in maintaining the pair-bond is its inhibitory role on partner preference formation (Aragona et al., 2006). It is thought that due to the increase in D1R expression no novel bonds can be established. It is assumed that in natural environments when an opposite sex conspecific is encountered DA is released in high concentrations and thereby activating the low affinity D1R (Robinson et al., 2002).

Besides changes in D1R expression, extended bonding also changes the V1aR expression and AVP turnover in the anterior hypothalamus (AH) of male prairie voles (Gorbrogge et al., 2009), and possibly DA (Gorbrogge et al., 2007). And the activation of AVP, inferred by antagonists, is necessary for the display of selective aggression (Gorbrogge et al., 2009). Unfortunately the mechanism that regulates female selective aggression has not received much attention.

In contrast to AVP, OT does not seem to have a role in selective aggression in either sex. In males, administration of OT or an OTR antagonist did not alter selective aggression (Winslow et al., 1993), and in females aggression is reduced by OT administration, even when given at very low doses (Witt et al., 1990). Also studies on maternal behavior suggest that OT is not necessary for maintaining the behavior in experienced mothers (Fahrbach et al., 1985).

As discussed in the previous section pair-bonding increases CRF mRNA in the BNST to quickly respond to social stress (Bosch et al., 2009). It is assumed that separation from the partner is stressful and in turn promotes partner seeking behavior. This is in accordance with the study by Carter et al. (1995) who found elevated levels of CRF after 24 hours of separation from the preferred partner. These CRF levels were below baseline level after reunion, while after 24 hours of separation interacting with stranger elevated levels of CRF.

In summary the maintenance of the pair-bond is dependent on selective aggression and the inability to form a novel pair-bond. These are dependent on the females reproductive status, increases in D1R and V1aR expression in males. The aversion to separation by changes in the HPA axis/CRF functioning promotes proximity seeking. The neural mechanisms that underlie behavior of the female in maintaining the pair-bond are an understudied area, but there is evidence that it relies on similar behavioral patterns.

In humans a relationship is to some extent maintained by a similar behavioral repertoire. An important difference is that in prairie voles the pair-bond is mostly maintained by hormones and sensory stimuli, while in humans cognitive and meta-cognitive mechanisms play a more prominent role (Machin & Dunbar, 2011). Clearly pleasure and satisfaction are

very important drives in maintaining relationships. For instance romantic love is a strong predictor of relationship stability (Acevedo & Aron, 2009). Imaging studies of people in long-term relationships also show activity in the reward system (Bartels & Zeki, 2000). For instance activity in the anterior cingulate, medial insula, striatum, NA and VTA was observed, which are the same areas that are active in the initial phase of romantic love (Aron et al., 2005). The participants in the longer relationships also reported very high levels of passionate love but they scored lower than those who recently had fallen in love. An interesting finding comes from a study by Acevado et al. (2012) who studied men and women in a relationship of ten years or longer, the phase in which compassionate love is predominant. They also found activation more areas than during the early-stage romantic love indicating that love changes over time. Because these participants were recruited to be still very passionately in love with their partner and also scored high on self-reported passionate love, it is the question whether these participants were reflect a typical sample of those who are in such long-term relationships. But it is interesting to note that passion does not have to wane in all relationships. For further research it is interesting investigate in far the brain activation differs and between those that are still passionately in love and those for who passion is low and the relationship is more dominated by compassionate love.

Also childhood experiences of parental love have an important influence. For instance most adults, regardless of their age, report a similar attachment style in their current or last romantic relationships as with their parents (Hazan & Shaver, 1987). It is assumed that when a secure attachment in the relationship is achieved the partner has a stress buffering role and thus has become a safe haven (Sbarra & Hazan, 2008). It is thought that this is (partly) the result of a conditioning of the stress buffering effect of the partner. This might explain why the stress related hormone levels have returned to normal during this phase (Marazziti et al., 1999; Marazziti & Canale, 2004). Also the self-reported feelings of stress and obsession were absent. In all cases the levels were indistinguishable from singles and those in a long-term relationship, These changes indicate that the falling in love phase (discussed in the previous section) is somewhat stressful situation, and it is assumed that as the relationships progresses the aversion to (prolonged) separation will cause proximity seeking of the partner, and therefore help maintain the relationship.

Another important overlap between human love and pair-bonding of prairie voles is the inhibiting role of the current bond on the formation of a novel bond. For instance when passionate love is reciprocated the automatic attention towards other possible love interests is decreased, while it is increased towards the partner (Korany & Rothermund, 2012;

Lundström & Jones-Gotman, 2009; Maner et al., 2008). Furthermore passionate love has an inhibitory role on feelings of passion towards other individuals (Berscheid & Meyers, 1996).

Also for humans mate stealing is not an uncommon process, which is done both by males and females (Buss et al., 2002). Therefore mate guarding is necessary to maintain the relationship. Although violent rejection of competitors is one of the ways in which humans can guard their mates, other tactics such as vigilance and possessiveness are more commonly used. Mate guarding is triggered by feelings of sexual jealousy, and mate guarding behaviors by males is highest at the peak moment of fertility of their partner (Gangestad et al., 2002). It is intriguing that mate guarding in prairie voles and humans is under some influence of reproductive fitness of the partner (Resendez et al., 2012). For females there is some evidence for the hormonal influences on mate guarding. For instance females that are on birth control report more feelings of sexual jealousy and perform more mate retention behavior than naturally cycling women (Welling et al., 2012). This effect is only observed in females that use contraceptives with high levels of estradiol, while there is no such effect for those who use contraceptives with high levels of progesterone. It is interesting that these two steroid hormones have opposing roles on mate guarding, because they can have opposite effects on OTR expression (Nissenson et al., 1978). Specifically estradiol increases OTR expression whereas progesterone has an inhibiting effect. Although OT is usually reported as pro-social, high levels of OT is also related to rejection of out-group members (De Dreu, 2012). Thus could implicate that OT plays a role in human pair-bond maintenance.

More direct evidence that OT is related to maintaining a relationship is that the high OT levels related to falling in love were not decreased during the six months later follow-up (Schneidermann et al., 2012). It is not yet investigated if these levels drop after a longer period. Also the initial OT levels were lower in those who had broken up compared with those who stayed together. Because the OT levels correlated with positive affective communication, affective touch and synchronization between the partners, the levels could provide to be an indirect measure of relationship quality. Furthermore there is some experimental evidence that OT in humans contributes to relationship maintenance. The administration of OT in men who were in a relationship decreased their responsiveness to an attractive female, while in single men the administration had no effect on their responsiveness (Scheele et al., 2012).

In summary in humans, in contrast to prairie voles, there is evidence that a relationship is maintained by OT. Also in humans and prairie voles the partner functions as a safe haven and separation aversion promotes proximity seeking. Furthermore activity in the

DA circuitry is implicated in humans and prairie voles, and in humans is related to (still) being passionately in love. But in contrast to prairie voles who remain together for life, humans can fall out of love and in turn end the relationship. Unfortunately very little research has been performed on falling out of love, thus only the impact of such a separation will be discussed in the following section.

2.6 Pair-bond disruption and dissolution of relationships

Since only a few mammalian species are monogamous, little is known on the factors involved in mate desertion in monogamous mammals (Renfro et al., 2009). The most incidences of pair-bond disruption in prairie voles is by death of the partner, only in very few instances the disruption is due to mate desertion (Carter et al., 1995). Field studies indicate that when a pair-bond is disrupted, only 20% of females form a new pair-bond, but almost all females remain reproductively active (Thomas & Wolff, 2004). The failure to form a new pair-bond is partly caused by the aggression due to the established pair-bond (although the partner is gone) and to protect the offspring. But a more important factor might be that these females are less desirable mates. In natural situations plenty of sub-adult females are available thus the male does not have to provide care for offspring that is potentially not his (Thomas & Wolff). Furthermore these widowed females are only receptive for a brief period, shorter than the established time-frame for the hormonal changes to establish a pair-bond.

An interesting laboratory study was performed by Getz et al., 1981. An voles that had an extensive pair-bond (living together for three weeks) were separated. The females were then housed with a novel male and formed a new pair-bond (living together for eight days), while the males were housed with unfamiliar males. When the original bonded male was reintroduced, the female reacted aggressively towards him. These females showed no aggressive behavior towards their novel partner, and both males did not initiate aggression towards the female. This might indicate that the separated males were still bonded, and that in the females the previous bond was overwritten. Also it appears that partner preference is unlearned after ten days of separation (De Vries, unpublished data in Carter et al., 1995), unfortunately it is unknown what brain-plasticity underlies this reversion and if there are any sex differences.

Unfortunately no studies have been done to assess whether selective aggression persists after prolonged separation from the partner. In the studies by Aragona et al. (2006), and Gobrogge et al. (2007) the partner was removed on same day as testing.

A few studies in prairie voles have investigated the effects of social loss, but rarely the

selective effects of pair-bond disruption have been investigated. As discussed above, pair-bonding alters CRF tone to prime the brain to respond quickly to social stress and promote partner seeking (Bosch et al., 2009). It seems that prolonged social isolation induces depressive like behavior and is linked to CRF immunoreactive neurons in PVN (Grippeo et al., 2007a; b). The only study so far that compared isolation from a sibling versus the preferred partner was done by Bosch et al. (2009). After four days of separation from the partner, passive stress coping was increased in the forced swim test and tail suspension test, while no effect was found for those who were separated from the sibling. The effects of these behaviors were reversed by providing a CRF-R1 and/or a CRF-R2 antagonist during the isolation. These antagonist had no effect on passive stress coping when they administered to voles that had remained with their partner. It is thought that the long-time separation from the partner is a chronic stressor and causes the HPA axis to become overactive.

For humans the end of a relationship can have serious negative consequences, the end of a relationship is related to the onset of major depression and other mental health problems (Davis et al., 2003; Monroe et al., 1999). It is thought that following a separation someone goes through two stages, first protest to reestablish the bond, and when protest fails, withdrawal and despair, which might function to promote detachment (Bowlby, 1980). During the protest phase the one who was rejected might actually be more in love than before the separation, as adversary can increase romantic passion, this is termed frustration attraction (Fisher, 2004). Subsequently when it becomes clear that the bond will not be reestablished the despair phase sets in, the feelings in this phase are dominated by depression and lethargy. Sbarra and Hazan (2008) propose that protest is a disorganized response to the loss of the coregulatory reward process related to the pair-bond, and after a while despair sets in which is reliant on an organized response involving the HPA axis. In order to overcome this despair phase the lost state of security must be regained.

So far, three studies have investigated the neural correlates of a break-up. Fisher et al. (2010) found activation in the VTA and striatum which was related to still being in love with the ex-partner. The specific areas are implicated in processing uncertain rewards and delayed responses. They argue that the activity in these reward areas is related to the motivation to reestablish the bond with the ex-partner. This could indicate that these subjects were in the protest phase. It is interesting that the activation strength in these areas was negatively correlated with time since the break-up. This implicates that the rewarding effects associated with attachment decrease across time.

In contrast to the study by Fisher et al. (2010), the other two other studies found a

decrease in activity in the ventral striatum/accumbens, and more activity in areas related to depression (Najib et al., 2004; Stoessel et al., 2011). The individuals in these two studies were tested a longer period after their break-up and were generally more accepting the situation than the participants in the study by Fisher et al.. Also the subjects these studies were instructed (Najib et al.) or permitted (Stoessel et al.) to ruminate on the loss, and felt a mixture of sadness, anger and anxiety, and reported no pleasant feelings when viewing pictures of their ex-lover. On the other hand in the study by Fisher et al. the subjects had to focus on the positive memories. Due to these differences in methodology it is hard to compare these studies, but it is tempting to conclude that the participants in the study by Fisher were in the protest phase, and that the activity in the DA rich areas is related to the motivation to reestablish the relationship. In contrast the participants in the two other studies could be in the despair phase, and that the decreased activity in these areas reflects a depression of the reward system. The subjects in these studies scored at clinically relevant levels of depressive symptoms and might be the result from the prolonged suppression of the reward system (Davey et al., 2008). Unfortunately in the prairie vole model the effects of pair-bond disruption on the reward system have not been studied, so it is unknown if pair-bond separation first activates the reward system and during the despair phase depresses it.

Also Interesting in the study by Fisher et al. (2012) it that activity in the VP, an area rich in V1aR, was decreased and showed a negative correlation with time since the break-up. In contrast this area showed increased activation in the study by Aron et al. (2005), and correlated with relationship length in those who recently had fallen in love. This overlap suggests that the attachment related responses decrease across time.

3. Brain areas & Endocrine factors in addiction

3.1 Drug addictions

Drug addiction is considered to be a chronic medical disorder which is the result from pathological changes in brain functioning (Kalivas & O'Brien, 2008). Although all drugs of abuse have their own chemical composition and have their unique way of influencing the brain, it is considered that there is a core process in addiction. This core process is assumed because addiction to all kinds of drugs result in the same behavior, the loss of voluntary control over the substance use, and a decrease in interest in other activities. This core process is the hijacking of the system established for an adaptive hierarchy of behaviors that ensure survival.

The main areas implicated in addiction are the dopaminergic projections from the VTA to the NA, VP, amygdala and cortical areas (including PFC, OFC and ACC) (Feltenstein & See, 2008; Koob & Volkow, 2010). see figure 3 for an overview.

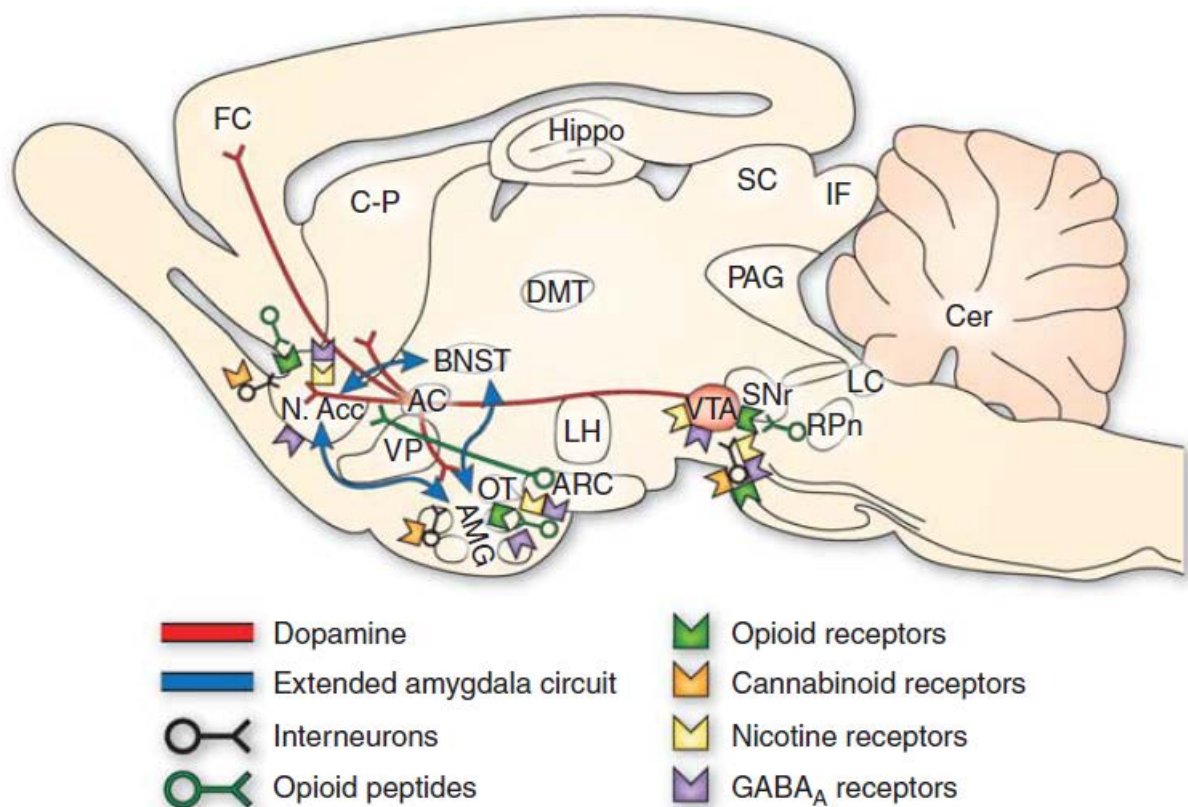


Figure 3, areas implicated in the acute effects of drugs (in the rat brain). Important areas are the ventral tegmental area (VTA), caudate putamen (C-P), Nucleus accumbens (N. Acc) frontal cortex (FC) and the amygdala (AMG) (Copied from Koob & Volkow, 2010).

Before the factors involved in addiction are discussed, it is important to note that in comparison to the research on love and pair-bonding (discussed in chapter 2) much more research has been devoted to addiction from many different fields. For instance there are abundant experiments on animals, human imaging studies, genetic mapping, and the pharmacological impact of drugs. Therefore the picture of addiction is vastly more complex and has led to the development of many different theories on the development of addiction. It is outside the scope of this thesis to compare the different theories, but none of them can fully explain the whole process of addiction (e.g., Ivlieva, 2012; Zernig et al., 2007).

Two prominent theories will be discussed; first the incentive salience theory developed by Robinson and Berridge (2003; 2008), which assumes that the drug causes the dopaminergic system to become hypersensitive to the drug and the associated cues. This hypersensitivity manifests itself as a pathological ‘wanting’ of the drug. And second the allostasis opponent process theory developed by Koob and Le Moal (2001; 2008), which assumes that in order to regain homeostasis, the impact of a drug is counteracted by an anti-reward process. With chronic drug use this anti-reward process becomes overactive and results in a new homeostatic set-point of the reward system (they call this process allostasis). These two theories are not necessarily mutually exclusive, and probably explain different parts in the whole process of the development and maintenance of addiction. The two theories can be combined if it is assumed that in addiction the sensitivity of the reward system decreases for both natural and drug stimuli, but that the decrease for natural reinforcers is stronger than for drugs (Heyman, 1996; Zernig et al., 2007). Or that the ceiling effect of incentive salience of the drug (which happens during the initial drug exposures (Vanderschuren & Pierce, 2010)) is reached before the new allostatic set-point of the reward-system (or that this process continues for a longer time) and/or the PFC also has to be affected before the behavior has become compulsive. Whatever the case, the starting point of both theories is the same; drug use starts out as voluntary and becomes compulsive with extended use.

On a final note only a minority of those who use a drug repeatedly will ever become addicted (Heyman, 1996; Müller & Schumann, 2011). So it is important to consider that the combination of an individual vulnerability and the repeated use of a drug is necessary to develop an addiction. It might be that certain of these vulnerabilities are further enhanced by the impact of the drug, so in some cases it the question what part is the cause and what part is the consequence of addiction.

3.2 Behavioral addictions

Recently it has been argued that besides drug addiction the view should be broadened to incorporate behavioral addictions, such as gambling, sex and physical exercise addiction. These behavioral addictions share the same psychological and behavioral patterns as drug addiction, for instance, craving, impaired control, tolerance, withdrawal, and high rates of relapse are also part of these behavioral addictions (Olsen, 2011). Despite the overlap in symptoms it is debated to what extent behavioral addictions are actual addictions. This debate is hindered by two important obstacles, many theories of addiction involve the chemical impact of drug consumption on the brain, and the definitions of most behavioral addictions are not well established, which makes it problematic to compare studies (Karim & Chaudhri, 2012). Although it is debated, a number of researchers advocate that both types of addictions are the result of neuro-adaptations in the same circuit (e.g., Alcock, 2005; Holden, 2001; Olsen). There is ample evidence that this neural circuitry can be altered without drug taking (Holden), and that changes by behavior are even vital, because the system functions to perpetuate behaviors that are essential for survival (Alcock). Other evidence comes from fMRI studies indicating that the same areas are activated in both types of addictions (Karim & Chaudhri) also several pharmacotherapies that are used for the treatment of drug addiction are effective for treating non-drug addictions (Olsen). With this considered the following definition of addiction will be postulated.

3.3 Definition of addiction

In this thesis it is considered that in both behavioral and substance addictions the brain chemistry is altered in a similar manner. With this in mind the following **definition of addiction** will be postulated: *Be it a behavior or a drug, addiction is the compulsive use of a drug or compulsive behavior, characterized by a loss of control over the drug use/behavior despite negative consequences and a reduction in the drive to obtain other (natural) rewards. The development of addiction is the result of specific changes in the brain (neuroplasticity). In the initial phase drug use is under voluntary control (non-addicted) and with repeated consumption or performance of the behavior changes into compulsive drug consumption/behavior (addicted).*

3.4 Animals and humans

As discussed before, it is hard to establish which parts in human studies are cause or consequence of addiction, thus the modeling of addiction in animals is essential. These animal models provide the opportunity for experimental manipulation of the brain. It is important to note that it is considered that no full animal model of human addiction can be made, but separate features such as escalation of drug use, tolerance, withdrawal and craving can be studied (Koob & Volkow, 2010). Also the observed changes in the brain of these animals can depend on a variety of factors such as the type of drug, dosage, duration of use and behavior used as criteria for drug addiction.

The animal model with the highest face validity of human addiction is the self-administration model (Koob & Volkow, 2010). Escalation of drug intake is observed when animals have long time access to a drug during a session (six hours), while drug intake remains stable when animals have only one hour of access to the drug during a session (Ahmed & Koob, 2005). Furthermore it is assumed that the changes in the brain of animals (to some extent) also happen in humans.

3.5 Development of addiction

For the development of addiction it is assumed that the neuroplasticity of addiction consists of two phases, during initiation there are transient changes in neural functioning continuing for hours up to weeks during abstinence, and in this phase drug use is completely deliberate and voluntary (regulated relapse) (Kalivas & O'Brien, 2008). During this phase drugs are used as instruments to change a mental state (Müller & Schumann, 2011), for example, drinking alcohol to relax, or taking XTC to increase sociability. Drugs are both pleasurable (are interpreted as positive by the brain) and are positively reinforcing, leading to a repetition of drug consumption (Hyman & Malenka, 2001). While during the second phase, there are “stable changes” in neuroplasticity which last for weeks up to permanency, which should underlie addiction (Kalivas & O'Brien). That these changes are stable is fundamental for the maintenance of the addiction, and are responsible for relapse after a period of abstinence. The factors involved in the shift from regulated to compulsive use will first be discussed.

It is important to note that in pharmacological terms certain aspects of the drug can undergo tolerance (decrease in effect), sensitization (increase in effect) or do not change (Robinson & Berridge, 2003). Because most changes caused by drugs are transient, and usually revert back to normal after time (Kalivas & O'Brien, 2008), probably caused by homeostasis. For instance tolerance to the hedonic impact develops because receptors that are

continuously activated reduce their sensitivity or are down-regulated to counteract the effects thereby maintain the homeostatic balance (Lees & Lingford-Hughes, 2012). By this decrease in effect more of the drug is needed to get desired effect. Because tolerance can already be observed in non-addicted individuals, is not a necessary criterion for addiction (Kalivas & O'Brien, 2008).

All drugs all have their own specific impact on the brain, but have in common that they directly or indirectly increase DA in the mesolimbic pathway, especially in the NA or ventral striatum (Lees & Lingford-Hughes, 2012; Volkow et al., 2012), But also DA from the VTA to the PFC amygdala is implicated (Vanderschuren & Kalivas, 2000). The DA release by drugs is up to ten times greater (beyond physiological limits) and has a longer duration than natural rewards (Kalivas & O'Brien, 2008; Wise, 2002).

The two main types of dopamine receptors: D1R and D2R have opposing roles in addiction (Volkow et al., 2012). D1R is important for drug reward, while D2R is thought to interfere with drug reward. For instance monkeys in with high D2R expression in the NA self-administer less cocaine, or alcohol than those with a low D2R expression (Volkow & Li, 2004). It can be that the low D2R levels are a predisposing factor for the vulnerability to develop addiction. Importantly with chronic drug use the expression and/or sensitivity of these receptors might be further altered.

It is thought that DA's role is essential for the motivational ('wanting) aspect of rewards (Berridge & Robinson 1998; Robinson & Berridge 2003), while the hedonic ('liking') aspect of reward is dependent on the endogenous opioids and/or cannabinoids (Nestler, 2005a; Volkow et al., 2012). Both play a role in reward related learning which consists of three aspects: 'liking', 'wanting' and associative learning. In the incentive salience view DA first responds to the UCS (rewarding stimulus) reflecting the reward is wanted, it is not responsible for liking (or the modulation thereof) nor is it responsible for the associative learning process (Berridge & Robinson 1998). With repeated use DA is triggered by the drug paired cues (CS) and in turn cause a wanting of the reward. The role of

Drugs cause the system to become oversensitive to these incentive cues and increase the 'wanting', while 'liking' might be decreased due to tolerance. This leads to a disproportionate degree of 'wanting' of the drug, which can manifest itself both conscious as craving and unconscious (Robinson & Berridge, 2003; 2008). Also it is important that the incentive salience of the drug reaches a ceiling effect already early on in drug taking (Vanderschuren & Pierce, 2010). Furthermore once the incentive salience has been acquired it is long-lasting. It is important to note that incentive salience does not equal addiction. It

seems probable that for this exaggerated 'wanting' (in humans) to become the compulsive drive of drug consumption (addiction), the PFC which exerts top-down control over the subcortical input (Heyder et al., 2004), also has to be affected. The influence of drugs on the PFC will be discussed in the last part of this section.

The impact of a drug is assumed to recruit an opposing force that decreases the impact of the drug in order to regain homeostasis (Koob & Le Moal, 2008). This opposing process, termed the anti-reward process, is assumed to happen within the dopaminergic system and as well in another system that is responsible for the withdrawal syndrome after the drug use is discontinued (which will be described later on).

Normally reward (wanting) sensitivity which is measured by electrical self-stimulation is under homeostatic control and is stable over time (Ahmed & Koob, 2005). Drug consumption causes a temporary decrease in the reward thresholds of self-stimulation, while during withdrawal the responsiveness increases and slowly returns to baseline levels. If a drug is repeatedly consumed before this anti-reward process has worn off, it might become enhanced and cause a decrease in the responsiveness of the DA system in general, resulting in a new homeostatic baseline set point for the reward threshold (A process they call Allostasis) (Koob & Le Moal, 2008; George et al., 2012). This process has been demonstrated by the progressive and persistent elevation of the baseline reward threshold when the self-administration of drugs escalate in rats (Ahmed & Koob). In contrast the baseline threshold is not changed in animals that maintain stable (low) drug consumption. Due to this elevation in the reward threshold, natural reinforcers are less efficient to activate the system. It is assumed that this decrease in responsiveness of the DA system causes the feelings of anhedonia (or perhaps better termed amotivation) which normally coincides with drug withdrawal. But with escalated drug use the depression of the reward system can persist for a very long time.

In summary it seems that the brain first seems to become more sensitive to the drug and the associated cues, but then in turn becomes insensitive to all cues. When identifying a common mechanism of all drugs of abuse Nestler (2005a) concluded that most drugs of abuse result in a decrease in basal DA functioning (tolerance/homeostatic adaptation) but also sensitized response to drugs and associated cues. This provides evidence for both the incentive salience theory and the Allostasis opponent-process theory.

PET studies in human addicts have consistently shown a decrease in D2R, and less DA in striatum after acute and protracted withdrawal (Volkow et al., 2009). Also in addicts compared to healthy controls amphetamine resulted in lower DA release in the ventral

striatum and putamen (Martinez et al., 2007). These changes can be interpreted as an indication of a decrease in baseline functioning of the system. Although it should be noted that recently it has been demonstrated that D2R can have two affinity states D2^{high} (functional state for DA) and D2^{low}, which cannot be distinguished with the radiotracers used in PET. It might happen that even if the total D2R expression is decreased the system still reflects a sensitized state by expressing more D2R^{high} than D2R^{low} (Robinson & Berridge, 2008). Although this option is possible, I assume that the chronic exposure to a drug results in a reduction of D2R expression, and (at least for cocaine) in an increase in D1R (Burkett & Young, 2012). Thus the signalling in the DA pathway is altered in more D1R than D2R.

Furthermore it is assumed that withdrawal is a part of the anti-reward process (Koob, 2010). Withdrawal produces a stressful, aversive, anxiety-like state after drug consumption is ceased. This process with normal use also returns to baseline levels after a time. But also here it is assumed that with the chronic drug consumption the baseline functioning changes due to Allostasis. This process happens in the extended amygdala, which normally integrates stress/arousal states with hedonic processing (Koob & Volkow, 2010). The extended amygdala consists of the CeA, BNST, and a part of the NA (Koob & Volkow, 2010). Notably drugs impact the transmission from the VTA to these areas. The negative state during withdrawal is mediated by CRF, noradrenaline (in BNST) and dynorphin in the NA and amygdala (Koob & Volkow, 2010). The activation of D1R and/or D2R can directly or indirectly affect the release of these substances (George et al., 2012).

In general the withdrawal state is insufficient to explain relapse after the withdrawal symptoms have faded out (Robinson & Berridge). But the aversive state might at least be partly responsible for continued (not necessarily compulsive) drug taking, but marks the shifts from positive reinforcement to negative reinforcement. Furthermore the Allostatic shift in CRF functioning might explain the high levels of stress reactivity that are still observable after protracted periods of abstinence. The impact of this increase in stress reactivity will be further discussed in the section on abstinence and relapse.

Another important acute effect of drugs is to suppress some neural processes in the PFC (Ivlieva, 2012). It seems that with repeated use more regions are affected by the drug. For instance in monkeys initially cocaine only affect the vmPFC and OFC, while after repeated use the drug also affects more rostral and later portions of the PFC (Beveridge et al., 2008). Importantly chronic drug administration in animals results in the behavioural symptoms of PFC dysfunction (Robinson & Berridge, 2008). These effects have been

associated with a reduction in the D2R expression in mPFC of rats after escalated drug use, while D2R in the mPFC is unaltered with limited access (Briand et al., 2008). It has been implicated that these changes in PFC functioning should result in less inhibitory control over the behaviour. Taken together the gradual decrease in PFC functioning could underlie a decrease in effectively controlling subcortical impulses, the 'wanting' of the drug. Once the PFC is compromised the drug use has become compulsive. Importantly in humans PFC dysfunction might already be a pre-existing vulnerability which can be further exaggerated by addiction.

Thus drugs can increase their own motivational impact, lead to an aversive withdrawal syndrome (that helps maintain drug addiction in some degree by negative reinforcement), and decrease the reactivity of the reward system which decreases the interest in other rewards. With extended use the homeostatic set-point of reward-system seems to be decreased, while it is increased for the stress system. Furthermore extended drug use can result in PFC dysfunction which leads to a decrease of inhibitory control. How these changes in the brain help maintain addiction will be discussed in the next section.

3.6 The maintenance of addiction

As discussed in the previous section the chronic administration of a drug causes neuro-adaptations in systems for reward, stress, salience, motivation, and executive functioning. Once addiction is developed D2R expression (and for some drugs) is decreased, and for some drugs D1R expression is increased, within the meso-cortico-limbic system (Burkett & Young, 2012). The increase in stress reactivity is presumed to be the result of an increase in the baseline CRF functioning in the extended amygdala (Koob, 2010). And furthermore a decrease in PFC functioning is observed, which is related to a decrease in inhibitory control (Goldstein & Volkow, 2002; Kufahl et al., 2005). These changes underlie the maintenance of the behaviour. Drugs are still consumed even when cognitively appraised that the behaviour is unhealthy or when there is the motivation to not use drugs anymore (Sellman, 2010). Also in many cases addicts report not even really 'liking' the drug anymore (by the development of tolerance for the hedonic impact), thus drug consuming behaviour is compulsive.

The drug seeking and consumption is now driven by the excessive 'wanting' of the drug which can manifest itself both consciously as craving, and unconsciously (Robinson & Berridge, 2003). This 'wanting' is an irrational desire, because it is not really pleasure driven, Similar effects of irrational 'wanting' have been observed in humans that had electrodes implanted in limbic sites which they continuously stimulated resulting in feelings of wanting

without reporting any liking (Berridge & Kringelbach, 2008). Especially important factors that trigger the ‘wanting’ are the drug associated cues (Robinson & Berridge, 2003).

In contrast to the non-addicted state these feelings of ‘wanting’ are less efficiently controlled by the PFC. There is ample evidence of a reduction in PFC fMRI activity in addicts of variety of drugs, which include the ACC and OFC (Goldstein & Volkow, 2002; Kufahl et al., 2005). These areas are involved in inhibitory control. It is important to note that self-control exertion is a limited resource function (Muraven & Baumeister, 2000), and it might be that these resources are easily depleted in addicts. These reductions in cortical functioning are linked to less D2R binding in the striatum of human addicts (Volkow et al., 2009). Importantly D2R decreases in animal models after drug use escalation are related to disruptions in reversal learning, working memory and sustained attention (Koob & Volkow, 2010). Thus it seems that DA is less able to correctly modulate PFC activity anymore. (Volkow & Fowler, 2000).

Furthermore the reduction in baseline functioning of the DA system due to allostasis the D2R expression and DA release in the striatum are depressed by the chronic drug consumption (Koob, 2010; George et al., 2012; Volkow et al., 2009). This decrease in the DA system probably reflects the high a-motivational state to obtain (other) rewards. It might be that the functioning in the whole system is decreased, but the decrease is relatively less for the drug of abuse than for other rewards (see Heyman, 1996). For instance this impairment can be demonstrated by the greater activation in the reward areas of addicts when viewing drug related cues than in controls. But importantly the response to natural rewards is impaired in drug addicts (Garavan et al., 2000). And furthermore addicts show reduced DA release to stimulants compared to healthy controls (Martinez et al., 2007).

Also drug use is can to some extend be maintained by the stressful, aversive, anxiety-like effects of withdrawal. It has been shown that stress promotes drug taking and disrupts self-control (Heatherton & Wagner, 2011). The acute withdrawal is regulated by CRF. For instance this has been demonstrated by the effects of a CRF1R antagonist or the combination of a CRF1R/CRF2R antagonist that decrease place aversion during withdrawal (Stinus et al, 2005; Heinrichs et al, 1995). But importantly withdrawal effects can be overcome by drug consumption, thereby creating the basis of negative reinforcement on drug consumption (Koob, 2010). Withdrawal is probably not the most important aspect of maintaining drug addiction, as the excessive ‘wanting’ probably plays the most important role, it can still be a contributing factor for maintaining drug use (Robinson & Berridge, 2003).

In summary these studies suggest that drug addiction is maintained due to the

irrational 'wanting' of the drug. This 'wanting' cannot be correctly inhibited anymore by the PFC, and there is a decrease in the motivation to obtain other rewards and negative effects of withdrawal and an increase in stress-reactivity. How these factors are implicated in abstinence and relapse will be further discussed in the following section.

3.7 Abstinence and relapse

When drug use is discontinued and the acute aversive effects of drug withdrawal have subsided the stable changes that maintain drug addiction are still present. These changes can persist for years, perhaps forever (Robinson & Berridge, 2008). Due to the long-lasting nature of these changes, even after protracted periods of abstinence, relapse can occur (Langleben et al., 2008).

It is thought that during abstinence drug seeking behavior is not erased, but actively inhibited, in a similar manner as fear conditioning responses are inhibited (Millan et al., 2011). This inhibition can be overcome by drug priming, drug cues and/or stress, which all activate a common relapse circuit (Bossert et al., 2005). For instance the neutral stimuli that were paired with the drugs still have their acquired motivational salience and cause DA release when encountered (Volkow et al., 2009). In turn this DA release will trigger the feelings of 'wanting' (Robinson & Berridge), or in an alternative view even directly trigger drug seeking behaviour (Alacro & Panksepp, 2011). A very important challenge in remaining abstinent is that after a period of abstinence the sensitivity to drug associated cues is further increased (Koob & Volkow, 2010).

Some effects, such as dysphoria, distress and sleep disturbances persist over long periods of time after drug use cessation (Koob & Volkow, 2010). These are probably related to the depression of the reward circuitry marked by the lower DA turnover and reduction in D2R expression in the striatum (Koob & Volkow, 2010; Volkow et al., 2009). These reductions are associated with feelings of anhedonia, mostly reflecting a decrease in interest and blunted motivational impact of normally rewarding stimuli.

Furthermore abstinence is marked by high levels of stress reactivity (De Witte et al, 2005; Valdez et al, 2002). This high stress reactivity is the result of the increased baseline functioning of the CRF in the extended amygdala (Koob, 2010). Furthermore it appears that norepinephrine, and cortisol are also overactive after protracted abstinence (Koob, & Le Moal, 2008). These overactive systems might make the abstinent user very vulnerable to stress. And stress, as stated before, is risk factor for relapse.

Also after protracted detoxification the hypo-functioning in frontal regions persists,

which are areas implicated in a decrease in inhibitory control and increased impulsivity (Koob & Volkow, 2010). It might be that this decrease in PFC activity causes some individuals to overestimate their ability to control drug use after a period of abstinence, that just one drink or hit cannot hurt, but in turn relapse.

Thus in summary even after a period of abstinence the brain is very sensitive to the drug associated cues that can cause extreme feelings of wanting, also anhedonia, high stress reactivity and decreased cognitive control can all contribute to relapse.

Although it is unclear if addiction can be reversed (or cured) after prolonged abstinence, several studies indicate that (at least some) of the effects of addiction can be reversed. Some executive functions can be recovered. In drug dependant individual who were abstinent for several months no differences in performance on an inhibitory control task or total brain fMRI activation was found when compared to controls (Bell et al., in press; Morie et al., in press). Implicating that at least some part of a very important function can be regained, the regulation of impulsive urges.

In the reward system recovery of DA turnover, transporters and D2R binding in the striatum is sometimes observed (Beveridge et al., 2009; Shi et al., 2008). Implicating that the effects of anhedonia associated with abstinence can also diminish over time. For D1R, studies in non-human primates provide mixed results, some showed increases while other showed decreases of D1R expression, while in human addicts no changes in D1R were found after abstinence (Volkow et al., 2012). In rats it seems that D1R in the NA shell transiently increases after discontinuing drug consumption (Conrad et al., 2010), and was normalized after 45 days of abstinence. While no changes of D1R in the core were found. So the recovery of the receptors might only happen in certain sub-regions. In general the time course of recovery of any function might depend on total drug consumption. For instance in monkeys who had one year of exposure to cocaine it was found that DA neurons were recovered in a subset after 90 days of abstinence, while some monkeys showed no recovery after twelve months (Nader et al., 2006).

To what extend these changes exactly help in staying abstinent and if addiction is fully reversible remain to be determined. However because relapse is a very common problem, even after prolonged abstinence, important factors in staying abstinent are controlling stress, as well as avoiding the drug and associated cues.

4. Discussion

4.1 Overlaps and differences between love and addiction

As discussed in the introduction many parallels between the behavior of people in love and those who are addicted can be drawn. In both addiction and love an external entity (drug or the mate) takes on special significance which results in robust goal directed behavior (Curtis et al., 2006). Because of this overlap many researchers have described the overlap between drugs and addiction (e.g., Burkett & Young, 2012; Insel, 2003), and even has lead certain researchers to propose that addiction is actually pair-bonding to the drug (McGregor & Bowen, 2012).

Clearly both love and drug use start out as positive and rewarding, and is continued due to positive reinforcement (e.g., Langeslag et al., in press, Müller & Schumann; 2011), which is related to DA activity in meso-cortico-limbic areas. Importantly relationships are usually continued by feelings of pleasure (Acevedo & Aron, 2009), while once addicted the drug use is continued despite not really liking the drug anymore (Sellman, 2010). Furthermore once a relationship has ended or drug use is discontinued feelings of anhedonia and stress emerge (Najib et al., 2004; Valdez et al., 2002). These feelings are related to a depression of DA activity and increases in CRF activity.

As can be seen in figure 4, both developing an addiction and falling in love rely on activation of, and changes in largely overlapping brain areas. Due to the social aspects of love/pair-bonding also the social neuropeptides OT and AVP in the LS and PVN are involved in the formation of the pair-bond and the subsequent maintenance (e.g., Schneiderman et al., 2012; Young et al., 2005). The roles of OT and AVP are mainly implicated in nurturance behavior, mate guarding and social memory (e.g., Aragona et al., 2007; Lim & Young, 2006). For addiction it has been suggested that chronic drug use also may cause changes in OT and AVP expression (McGregor et al., 2008). For instance amphetamine treatment in sexually naïve prairie voles causes V1aR overexpression in the AH, an area important for pair-bond maintenance (Aragona et al., 2007). Also in rats chronic administration of low doses of THC causes a down-regulation of OTR expression in the NA (Butovsky et al., 2006). It is unknown, if and to what extend such changes are responsible for drug addiction, but might implicate that drug abuse can result in social deficits. Furthermore it is interesting that the effects of social bonding and addiction on OT are in the opposite direction. Thus addiction might be related to an underactive OT system, while love is related to an increase in OT (Schneiderman et al.). Also it has been established that OT can have a protective influence on

some aspects of drug impact such as sensitization and tolerance (Kovács et al., 1998). This might provide why social factors are important protectors for developing addiction (McGregor & Bowen, 2012).

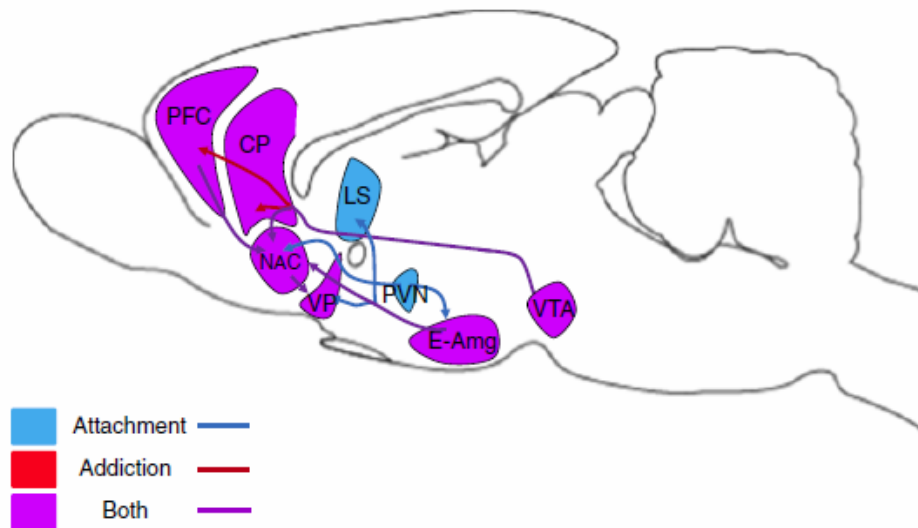


Figure 4. Overlap in the circuits of attachment and addiction. (Copied from Burkett & Young, 2012).

Despite this probably different involvement of OT and AVP, it is not necessarily enough to exclude the possibility that love is an addiction. In the following section a comparison will be made between the main events involved in the formation, maintenance and abstinence/relapse of addiction and comparing whether this also happens in love/pair-bonding.

4.1.1 Incentive sensitization

Initial drug use causes the brain system to become sensitive to the motivational impact of the drug and associated cues (Robinson & Berridge, 2003). It is important to note that sensitization is not necessarily addiction, and reaches a ceiling effect early on during drug taking (Vanderschuren & Pierce, 2010).

Sensitization is reflected by greater DA release with repeated exposure to a drug (Vanderschuren & Kalivas, 2000). In healthy humans the initial few drug exposures are associated with an increase in sensitized responding (marked by an increase in DA release) which can last up to one year after the first exposure (Boillieu et al., 2006). It is important to note that these individuals did not develop addiction during the experiment. Furthermore

sensitization does not result in an alteration of D2R expression (Pierce & Kalivas, 1997), which is usually found to be decreased in human addicts (Volkow et al., 2009). These decreases probably reflect the impact of chronic drug consumption, which will be discussed in the following section on Allostasis.

In love it has not been directly demonstrated that the repeated interaction with the partner increases DA release. But it is possible because fMRI scans reveal that falling in love and being under the influence of cocaine activate overlapping areas such as the ACC, insula, CN and putamen (Ortigue et al., 2010). Furthermore the activity in some reward areas is correlated with love duration, thus an increase in DA is possible (Langeslag et al., in press).

Also the early formation of incentive sensitization of a drug can spill over to other natural reinforcers and other drugs (Nocjar & Panksepp, 2007; Wyvell & Berridge, 2001). Unfortunately in prairie voles it has not been investigated if pair-bonding is also associated with a higher preference for other rewards. But in another monogamous species, the Titi monkey, pair-bonding is associated with an increase in the preference for a rewarding drink (Ragden et al., 2012). Also those just falling in love appear to be more reward oriented than singles, indicated by their performance on a reinforcement learning task (Brown & Beninger, 2012). Which might implicate that such a spill-over to other rewards also happens in love. But even if this happens, it clearly does not spill over to other potential mates, because the automatic attention towards them is decreased (Korany & Rothermund, 2012; Lundström & Jones-Gotman, 2009; Maner et al., 2008).

This sensitized response to drugs and the associated cues is thought to persist even after prolonged periods of abstinence (Robinson & Berridge, 2003). Importantly in abstinent addicts this sensitized responding is related to relapse. In love it is unknown if a sensitized response can be observed for a long time after a relationship dissolution. But it might be that in some individuals reminders of 'the one who got away' will still cause feelings of wanting to be together. Importantly abstinence causes a greater 'wanting' reaction by drug cues (Koob & Volkow, 2010). It seems that this wanting follows an inverted U-shape over time (called the incubation of craving) (Lu et al., 2004). Lu et al., think that these feelings of craving are very long lasting but not necessarily permanent. An interesting parallel can be drawn between the incubation of craving and reaction process after the disruption of an attachment bond (Bowlby, 1980). During the protest phase, which is related to reestablishing the relationship and thus with high feelings of 'wanting'. It could be that these feelings are even higher than before the bond was disrupted due to frustration attraction (Fisher, 2004). And with time as

the relationship is not reestablished the feelings of wanting go down during the withdrawal phase.

4.1.2. Allostasis in the dopaminergic system

With repeated escalated drug use there is decrease in the interest for natural rewards (Garavan et al., 2000). This is caused by a decrease in baseline activity of the reward system due to an exaggerated anti-reward process (Koob, 2010). Whether love also shifts the baseline function of the reward system has not been investigated. Probably if this even occurs in love, the decrease in natural rewards is probably in the same magnitude as in smokers, who do not give up their whole life to obtain or recover from the direct effects of smoking (although clearly the long-term health damage caused by smoking is another story).

PET studies indicate that during addiction D2R expression is decreased, and for certain drugs there is an up-regulation of D1R (Volkow et al., 2012). To my knowledge no PET studies on human DA binding or receptor expression have been performed during any stage of love. But on the basis prairie voles it seems that extended pair-bonding only up-regulates D1R expression (Aragona et al., 2003). Interestingly for both love and addiction, the balance between D1R and D2R signaling is increased in favor of D1R levels (Burkett & Young, 2012). Although it is unknown whether the shift in the D1R/D2R balance is within the same magnitude.

When an addict or someone who is in a long-term relationship views pictures or movies associated with their respective rewards many overlapping reward areas are still activated (e.g., Acevedo et al., 2012; Bartels & Zeki, 2000; Garavan et al., 2000). But in addicts the impact of a drug on the dopaminergic system is blunted in contrast to healthy controls (Martinez et al., 2007). Whether with time there is also a blunted DA impact of partner is unknown, but it is tempting to speculate should such an effect be found it is related to falling out of love.

Furthermore this depression of the reward system, due to Allostasis, is thought to be responsible for the feelings of anhedonia after discontinuing drug consumption (Koob & Le Moal, 2001; 2008). Such feelings of anhedonia are also seen after the dissolution of a relationship (Najib, et al., 2004; Stoessel et al., 2011). Importantly in addiction this anhedonia can persist for year after last drug use (Koob & Volkow, 2010). On the other hand it is assumed that after a relationship dissolution the feelings of anhedonia usually revert back to normal with time (thereby indicating that the baseline of the DA system has reverted back to normal levels. This is based on the assumption that the single control subjects probably had to

deal with heartbreak at some point in their life. But it might be that in some individuals this depression of the reward system persists and might be related to the development of major depressive disorder after a break-up (Monroe et al., 1999).

4.1.3 Stress and Corticotrophin-releasing factor

Falling in love is an uncertain time and is marked by stressful feelings (Marazziti & Canale, 2004), perhaps due to the uncertainty of this phase, but might also facilitate the formation of the bond (De Vries et al., 1995; 1996). For the development of addiction it might be that those who use a drug to cope with stress are more vulnerable to develop addiction.

Furthermore both love and addiction are maintained to some degree by the CRF system. In addicts withdrawal is stressful and consequently can lead to drug consumption (Heatherton & Wagner, 2011), whereas the stress buffering effect of the partner and/or the aversion to prolonged separation causes proximity seeking during love (Bosch et al., 2009; Sbarra & Hazan, 2008).. It is hypothesized that in addiction the CRF system becomes over sensitive as the result of the prolonged over-activity of the anti-reward process (George et al., 2012; Koob, 2010). And that this high stress reactivity persists after the acute effects of withdrawal have worn out. Furthermore the feelings of stress can cause relapse in addicts (Bossert et al., 2005).

There might be an interesting overlap in the upregulation of the CRF system. For instance pair-bonding alters the CRF tone in prairie voles, presumably to prime the brain to respond quickly to social stress (Bosch et al., 2009). Thus it is possible that the baseline functioning of the stress system is increased by pair-bonding. Furthermore if the partner is removed for a protracted period of time CRF activation might be further increased for a long time period (Grippo et al., 2007a; b). This increased CRF activity is related to depressive like behavior, and might be partly responsible for the depressive state after a break-up.

Importantly it might be that if chronically over activated the CRF system also might undergo an Allostatic shift in baseline functioning. It might be that those that also undergo this increase in CRF reactivity (combined with the continued depression of the reward system) are the ones that develop major depressive disorder after a break-up (Monroe et al., 1999). Also here it is also assumed that in most cases the stress system returns to normal levels after a while, perhaps because other individuals such as friends and family are used to take over the stress buffering role of the partner.

4.1.4 Changes in the prefrontal cortex

Another overlap is that addicts and those in love deactivations in higher order areas such as the lateral PFC and temporal cortex are observed. In those in love these deactivations probably cause a relative suspense of judgment towards the beloved, resulting in the 'love is blind'-phenomenon (Zeki, 2007). While in addicts it is considered that this hypo-activity of the higher order areas reflects a general decrease in inhibitory control (Volkow et al., 2012). Importantly in addicts the hypo-activity in these areas is also present during neutral tasks (Lubman et al., 2004). For those in love, although not investigated, it is not expected that during neutral conditions the higher order activity is blunted.

Thus drugs might even cause damage to PFC, which is not assumed to happen with love. This decrease in activity in the PFC of addicts might be the essential step in becoming addicted as the excessive 'wanting' of the drug cannot be really controlled anymore. This is because cognitive control is a limited resource function (Muraven & Baumeister, 2000), which in addicts is compromised. Especially important is that the drugs are still consumed even when cognitively appraised that the behaviour is unhealthy or when there is the motivation to not use anymore drugs are (Sellman, 2010). On the other hand in love there might also be a very high level of wanting, but might be better regulated in love (at least better than addicts can control their impulses). Interestingly males in a committed relationship with high levels of executive control respond less to flirting behavior of an attractive female (Pronk et al., 2010). While in singles executive control was unrelated to responding to flirting attempts. Importantly even when someone remains (for a while) in a relationship he or she wants to end this probably does not reflect an inability to control impulses. This actually is the complete opposite, to not just impulsively quit a once rewarding relationship.

4.2 The interaction between love and addiction

Thus addiction and love involve overlapping brain-areas, but how do the two interact? Importantly love is protective for the formation of addiction, and is related to lower levels of relapse during abstinence (Horwitz & White, 1991; Kosten et al., 1987). One interesting study investigated the impact of love on craving in smokers who were not attempting to quit (Xu et al., 2012). They did this by providing pictures of the partner coupled with smoking cues. Only in those who already reported moderate levels of craving before the experiment the picture of the partner was related to a decrease in craving. In contrast those who reported

already high levels, the picture of the partner had no effect on cue reactivity. This could implicate that love is helpful in those with milder symptoms, while those with more severe symptoms need other treatments to overcome their addiction.

In prairie voles the disruptive effects of drugs formation of the pair-bond can be directly observed. For instance amphetamine exposure induces selective aggression in sexually naïve prairie and inhibits partner preference formation (Gorbrogge et al., 2009; Liu et al., 2011). Which is probably due to the up-regulation of D1R by amphetamine. On the other hand extensive pair-bonding which causes the up-regulation of D1R in the NA of prairie voles, inhibits the rewarding effects of amphetamine (Aragona et al., 2006). Importantly it seems that the up-regulation of D1R by amphetamine and pair-bonding are the result of a different mechanism. In prairie voles amphetamine causes an accumulation of the D1R transcription factor DeltaFosB in the NA, while pair-bonding does not (Hostler & Bales, 2012). An increase of deltafosB in the NA is associated with increases in rewarding effects of the drugs. And importantly because deltafosB accumulates over time this is implicated in the development of addiction (Nestler, 2005b). Thus even though both drugs and pair-bonding result in a similar up-regulation of a receptor there can be different mechanisms involved, which in turn can have other effects such as differently altering gene expression.

4.3 Is love an addiction?

Taken together there are many similar changes in the brain in love and addiction, but even where they overlap it is the question whether these are within the same magnitude. Also despite of these overlaps in brain plasticity there are very important differences, especially in two main points that define addiction: the compulsive nature of the behavior and the decrease in the motivation for other rewards. There is little evidence that love results in compulsive behavior, it seems more likely that it is guided by a high level of motivation but is also clearly coupled with hedonic sensations, the participants in the studies all indicated pleasurable feelings associated with their beloved (e.g. Acevedo et al., 2012; Aron et al., 2005; Bartels & Zeki, 2000). Especially when falling in love the hedonic rewards from interaction with the partner might be very intense. The supposed decrease in interest in other rewards than the beloved, might reflect a general difficulty to regulate hedonic sensations that many individuals have (Frascella et al., 2010). It even seems that being in love is associated with an increase in reward orientation (Brown & Beninger, 2012).

Besides these empirical findings there are some problems with the definitions of addiction and love in general. Love has an adaptive function for species survival by providing

bi-parental care for the offspring to ensure greater survival (Fisher, 1998). While addiction is considered to be a chronic disorder (Detar, 2011; Le Moal & Koob, 2007), and might subsequently interfere with survival because the behavioral repertoire of addicts is mostly dominated by obtaining and using drugs while less energy is devoted to other nurturing behavior. This can be demonstrated by the high levels of child neglect by addicted parents (Regan et al., 1987). Furthermore love is reversible and possible to re-experience with someone else (Reynaud et al., 2010), is associated with many health benefits (Esch & Stefano, 2005). Also a stable relationship is protective for the development of addiction (Horwitz & White, 1991; McGregor & Bowen 2012) and associated with low levels of relapse during abstinence (Kosten et al., 1987). Addiction on the other hand is associated with a negative impact on health and increased risk of mortality (e.g. Haver et al., 2009; Hurt et al., 1996). Thus even if love would be an addiction it should be considered to be an ‘adaptive addiction’, which contradicts the definition of addiction.

Thus both the definition of addiction and the empirical findings do not provide strong evidence that love is an addiction. This conclusion does not rule out that there is a subset of people who are addicted to love. As for a variety of behaviors some individuals are considered to be addicted, such behaviors include sex, shopping and gambling (Karim & Chaudhri, 2010; Olsen, 2011). This also raises the possibility that those who are more often or longer infatuated or have problems moving on after rejection are a subgroup who are vulnerable for developing other addictions. The types of love that could be considered an addiction will be discussed in the following section.

4.4 Possible maladaptive forms of love as love addiction

Only a minority of people who use addictive drugs or indulge themselves in the behaviors that lead to behavioral addictions are addicted, or ever will become addicted (Heyman, 1996; Müller & Schumann, 2011). For love this could also be the case; some work has been done to identify problematic love, of which some might be considered an addiction. Some attempts have been done to provide diagnostic criteria for love addiction (see Reynaud et al., 2010; Sussman, 2010).

Love addiction can manifest itself as is repetitive and uncontrollable behavior, giving more than necessary attention and overly caring for the partner. Importantly this behavior is associated with feelings of loss of freedom, and a loss of interest in self-development and all other activities (Sophia et al., 2009). The core feature is the belief that romantic relations have some sort of magical properties, that every obstacle can be overcome by love (Sussman,

2010). It has been estimated that the prevalence of love addiction is around 5-10 % in the U.S. adult population (Timmreck, 1990). From the inventarisation of love styles by Lee (1978), two styles might be considered to be a form of love addiction: Mania and Agape. Mania is a very dependent and possessive style of love, while Agape is selfless all giving love. Both of these love styles are negatively related to self-esteem and are associated with a variety of psychiatric disorders, OCD, depression and anxiety, and case reports in substance dependent individuals (Sophia et al.). Further investigation by Sophia et al., revealed that the Mania style is related to high levels of impulsivity, and individuals were both high in reward dependency and punishment sensitivity. These persons usually maintained unsatisfying, even pathological relationships, and interestingly did not report a higher degree of love for their partner than controls. Sussman characterizes love addiction as a fixation on early phase of relationship (falling in love) and especially the obsession part. Unfortunately little is known about this addiction as no formal definition exists. Imaging studies that compare individuals with different love styles might provide more insight, and especially how they are mediated by attachment styles during childhood.

Another behavior that might be a form of love addiction is stalking (Meloy & Fisher, 2005). With stalking the behavior to obtain the object is very extreme, similar behavior is also seen in addicts that go through great dangers to obtain their drugs. Furthermore stalkers are obsessively pre-occupied with the one they stalk.

Males are far more likely than females to stalk, and they differ in their motivation for stalking. Females mostly stalk someone they are infatuated with, to establish a bond, while males mostly stalk a former romantic partner, to reestablish a dissolved relationship (Purcell et al., 2001). From a meta-analysis it appears that in 77% of the cases an acquaintance is stalked, and in 50% of all stalking cases it involved a former romantic partner (Spitzberg, 2002). Stalking has been linked to pathological narcissism, OCD (Meloy & Fisher) and a history of substance abuse (Purcell et al.).

Meloy and Fisher (2005) think stalking depends on an interplay between the serotonergic and dopaminergic systems. A similar reduction in central serotonin levels as in OCD patients is expected (Marazziti et al., 1999), which should account for the obsessive and impulsivity of stalkers. Also it is considered that those who stalk their ex-partner are in the protest phase of separation which is related an increase in the motivation to win back the former partner (Fisher et al., 2010). It is hypothesized that during the depression phase of a relationship dissolution stalking is less likely to occur. Unfortunately so far no imaging studies on stalking have been performed. These studies should provide more insight in the

underlying mechanisms of stalking behavior. It is possible that stalking is a behavioral phenomenon of an underlying disorder which is triggered by an inability to cope with romantic rejection.

Another form of love addiction could be related to the inability to adjust grief over the loss of a romantic relationship. Those who suffer from complicated grief report a persistent obtrusive longing for reunion with the beloved. In an fMRI study activation of the reward system was observed for complicated grievers but not in normal grievers (O'Conner et al., 2008). Interestingly the same areas are activated during drug cravings in addicts. This activation probably interferes adapting to the loss. What is especially interesting is that the activity in the reward-system was correlated with the intensity of yearning for reunion, but not with the time since death. It might be that complicated grief is the manifestation of love addiction during the despair phase.

These three types of behaviors are clearly maladaptive and could be different manifestation of love addiction. If this is the case, love addiction manifests itself in many different patterns of behavior. Therefore a diagnosis for love addiction should involve both the inability to control the behavior and the negative consequences the love has on the individual. Unfortunately these claims of love addiction are speculative as little research has been devoted to these maladaptive forms of love.

It should be noted that I do not claim that someone who stays in an unsatisfying relationship, has a high tendency to fall in and/or out of love, or has trouble moving on after a relationship dissolution is necessarily a love addict. There are many other reasons than love addiction that people stay together in unsatisfying or even abusive relationships. For instance certain social/cultural factors, such as stigmatization of divorce, staying together to raise children, or economic reasons could underlie the motivation to sustain unsatisfying relationships. Furthermore personality disorders and (psychiatric) illnesses can also play a major role.

4.5 Future research

Future research of human love should involve passionate love, maladaptive forms of love and try to identify love addiction as a disorder. Besides the question to what extent love and addiction overlap, it is probably more productive to further investigate how love is protective for the development and the treatment of addiction. The prairie vole model for human love is also an interesting model to study drug addiction. By using prairie voles the influences of the social environment on drug consumption and addiction can be studied, as well as the impact

of addiction on social behavior (Anacker & Ryabinin, 2010).

Also OT administration is proposed as a treatment for drug addiction (McGregor & Bowen, 2012). In rodents it seems that OT administration reduces alcohol consumption (Peters et al., 2013). and it seems that OT reduces the effects of DA, as the administration of OT does not result in conditioned place preference by DA administration in rats (Baracz & Cornish, 2013). Unfortunately enthusiasm for this type of treatment should be tempered because OT and AVP in prairie voles augments the DA signal rather than inhibits it (Insel, 2003). The tight coupling between the social system and the reward system could have different effects on the protectiveness of OT on drug abuse. Especially because it seems that animals with a more evolved social reward system are also more sensitive to the rewarding effects of drugs (Anacker & Ryabinin, 2010). Furthermore the acute effects of OT might be different than those after repeated use. For instance chronic intranasal OT administration in male prairie voles can result in OTR down-regulation and thereby resulting in social deficits, such as the inability form partner preference (Bales et al., in press). Despite these reservations the proposal by McGregor and Bowen warrants further investigation.

4.6 Conclusions

Both love and addiction rely on changes in the system for natural rewards. This is not strange because love is an adaptive behavior, while in addiction this system is hijacked. Although parallels between the behavior of those in love and addicts can be drawn, they are absent for two of the key criteria for addiction. In love a decrease in responsiveness for other rewards than the beloved has not been demonstrated, and love does not seem to be compulsive. Thus there is no evidence that love is an addiction. This conclusion does not exclude the possibility that in some exceptional cases people suffer from love addiction. Due to the lack of a definition for love addiction very little is known of its impact or treatment. Furthermore love is associated with improved mental health and better treatment outcomes for addicts. An interesting implication is to help rehabilitated addicts form and maintain healthy relationships in order to remain abstinent.

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