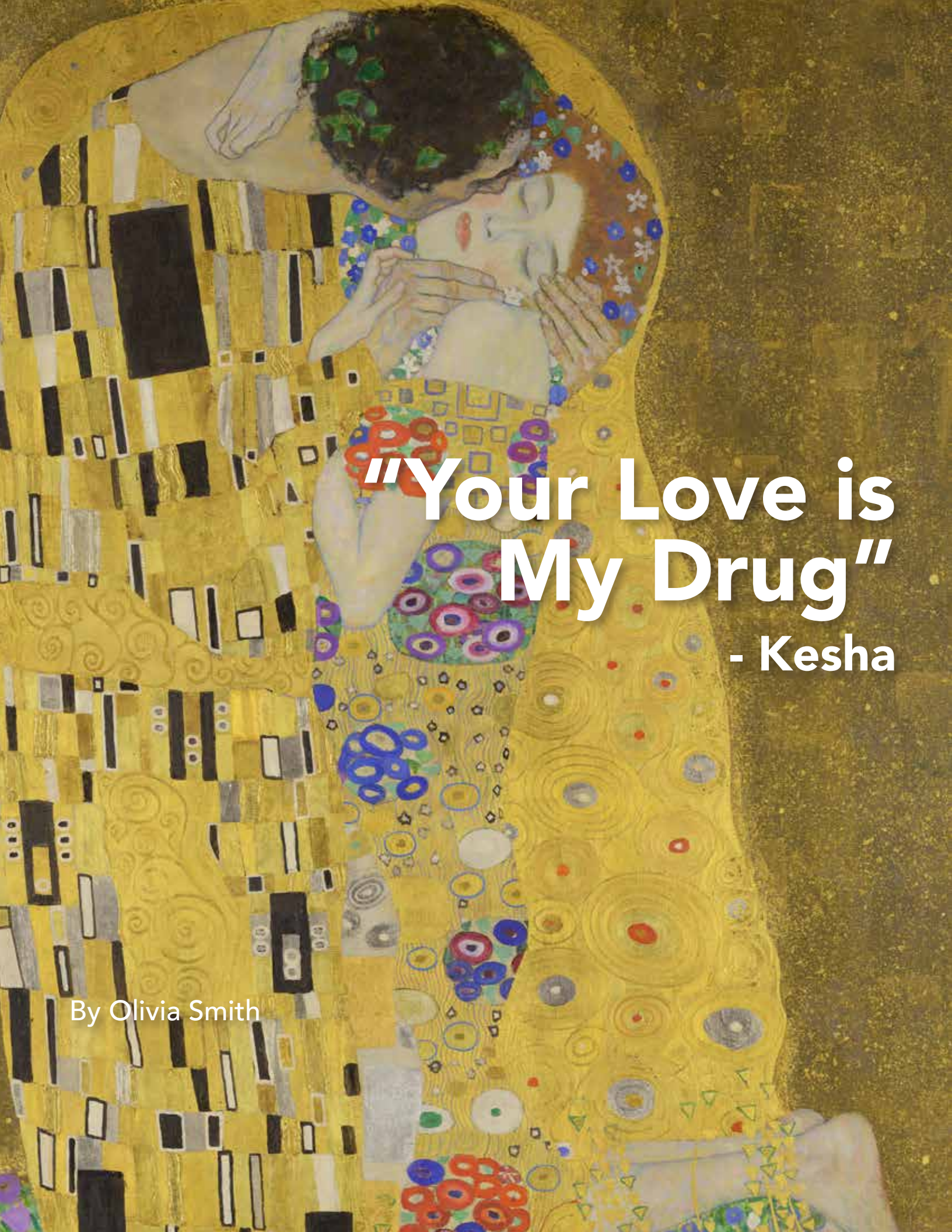

"Your Love is My Drug"

- Kesha

By Olivia Smith

"Can't Help Falling in Love" - (Haley Reinhart) Elvis Presley

"Ampelpärchen in Vienna, Austria" by Wikimedia commons user Qaswed. Lisenced under CC BY-SA 4.0.

Love for humans can seem so much more complicated than it seems to be for other vertebrates. Most human romantic love, however, can be explained by neurochemical processes. When you first meet someone you are attracted to, you may find yourself sweating and stuttering, with your heart beating a million miles a minute. These bodily reactions are actually signals from your brain. Essentially, there are three classifications of romantic love: lust, attraction, and attachment. Sets of hormones or neuromodulators that originate in the brain characterize each category. Romantic love is typically described as a feeling that has cognitive, emotional, sexual, and behavioral components and is focused towards a particular individual [1].

Romantic love is best understood as a motivational or goal-oriented state that gives rise to a variety of distinct sensations, such as euphoria or anxiety. Furthermore, romantic love does not include a brain system that is functionally specialized. Instead, a cluster of neural networks that converge on large areas of the caudate nucleus creating a flexible combinatorial map expressing motivating stimuli and memories. Depending on the individual and the circumstances, this may be the source of romantic love [2]. As a result, it would serve to illustrate the processing involved in a complicated human behavioral state that incorporates emotions. Together, the cortical, VTA, and caudate localization in participants who had been in a relationship for longer periods of time suggest that these regions are consistently and crucially involved in this aspect of human reproduction and social behavior, otherwise known as romantic love [1],[2]. So, obviously, all of these interconnected brain regions lead to a surge of all the emotions love can bring. Let's break it down!

"Bootylicious" - Beyoncé

The need for sexual fulfillment is what fuels lust. The desire to reproduce has an evolutionary foundation as well. The sex hormones playing a significant part in fueling this desire are testosterone and estrogen [3]. Lust is regulated by the preoptic area of the anterior hypothalamus, which is one source of gonadotropin-releasing hormone [4]. Gonadotropin-releasing hormone traverses a portal vascular system to the anterior pituitary to stimulate production of follicle-stimulating hormone and luteinizing hormone4. These two hormones then stimulate the gonads to produce the sex steroids, including testosterone, and testosterone can be metabolized to dihydrotestosterone, estradiol, and other estrogens [4].

Studies have shown that when testosterone is administered to castrated male rats, mice, or pigs, their sex motivation returns5. In humans, androgens are associated with increased sex motivation in both sexes. Women with higher levels of circulating testosterone have more sexual thoughts, greater desire for sex, and higher mean levels of sexual activity. Thus, there is compelling evidence that testosterone is associated with both male and female sex moti-

vation. Estrogen also plays a role in sex motivation. Rising levels of estradiol, a hormone made by the ovaries, cause female animals, including monkeys, to go into estrus (i.e., become receptive to sex) and engage in sexual activity [6]. Although there is limited evidence that higher levels of estradiol in human females are associated with increased sexual drive or behavior, some females claim to feel more seductive immediately before ovulation, when ovarian estrogen levels are at their highest. In aging males, small levels of adrenal testosterones convert to estrogen, which boosts their sex drive [4]. In reality, castrated male and female animals may engage in sexual activity when estrogen or testosterone is injected [4]. The link between testosterone and estrogen and how they interact with other biological systems is a complicated subject. However, it is evident that the neurological correlates for sex drive in mammals are distinct from those for attachment; whereas all mammals participate in sexual activity, only a limited number of mammalian species, notably monogamous prairie voles, develop long-term bonds to their spouse. More troubling is the connection between sex drive and attraction. Mammals frequently show the desire for sexual gratification, yet the majority favor some partners over others. This suggests that sexual desire and attraction are two somewhat different processes. Humans provide the most convincing evidence that these emotion systems are separate. We are capable of experiencing and expressing sexual desire both for persons to whom we have no romantic attraction and for those to whom we have no emotional connection.

"Let's Talk About Sex"
- Salt-N-Pepa

All vertebrates engage in sexual activity as a motivated action to maintain genetic diversity within a species and ensure its survival, according to a purely biological definition. Precopulatory phase, the initial stage of sex, is characterized by a variety of species-specific courtships and attractive behaviors [5]. The second phase, copulation, is the contact of male and female genitalia [5].

Both stages are controlled by the relationship between steroids, neuropeptides (such as vasopressin, prolactin, and oxytocin), and neurotransmitters (such as dopamine or serotonin)[4],[5].

"Good Feelin'"
- Flo Rida

Early-stage, romantic love is related to reward and goal-oriented brain areas. It is understandable why lovers express a need to remain with their romantic partner and to safeguard the connection with this new perspective on romantic love as a motivating state. An attraction for someone involves the mesolimbic "reward" pathway. Romantic love is not a distinct feeling in and of itself; rather, it attracts a motivation system including brain systems linked to motivation to obtain a reward [7]. A study using functional magnetic resonance imaging (fMRI) researched participants looking at a new romantic partner versus a random person. The results showed that when the participants looked at a beloved new romantic partner, specific activation occurred in the right ventral midbrain around the ventral tegmental area (VTA), dorsal caudate body, and caudate tail. These results provide strong evidence that these brain regions are associated with specific aspects of romantic love. The VTA contains dopaminergic cells that send projections to several brain regions, including the medial caudate and nucleus accumbens [4]. These regions play major roles in motivation and reward.

Consequently, attraction causes the brain to release copious amounts of dopamine and norepinephrine. These chemicals make us feel happy, energetic, and euphoric. Dopamine is a well-known player in the brain's reward path-

way. The hormone norepinephrine causes the more commonly known fight or flight response. Another hormone, adrenaline, is released when we feel stressed. Adrenaline and norepinephrine help us stay alert,fight, or flight. People in love have heightened brain activity in regions related to happiness and love. Brain scans of people in love show that these areas of the brain fire more when they see a photo of someone they are attracted to than when they see someone more random [4]. A decrease in serotonin may lead to a decrease in appetite and a more negative mood. However, females experience an increase in serotonin. These higher levels of serotonin can lead her to overthink about her romantic partners. In college dating terms, if your significant other tells you (female) that you are just being unrealistic and overthinking things, you're not crazy! Your serotonin levels are higher because you're in love and that's why you have obsessive thoughts.

A study used fMRI to compare the neural correlates of maternal and romantic love [4],[8]. The results showed that romantic and maternal love had some overlap in brain activation [4,8]. The putamen and caudate nucleus were found to be active together as well as the medial insular and anterior cingulate cortex. Romantic love activated the hippocampus, hypothalamus, and ventral tegmental area. The orbitofrontal cortex and periaqueductal gray area were activated for maternal love only [4],[8],[9]. The areas that showed the most activation were part of the mesolimbic pathway, which contains high densities of oxytocin and vasopressin receptors.

People who feel positive about their romantic partner tend to have higher levels of oxytocin in their blood. The elevated levels of oxytocin are associated with this reciprocity. Vasopressin receptor densities differ in brain regions. Monogamous prairie voles have higher numbers of vasopressin receptors in the medial amygdala, mediodorsal thalamus, and the ventral pallidum. Monogamous prairie voles first meet each other socially when they spend long periods of time cuddling with each other. Studies have found that when the two monogamous prairie voles are separated by a wire screen barrier, they do not form the same kind of relationships and prefer their partner over others.

Corticosterone in rodents is the equivalent to cortisol (the stress hormone) in humans. Basal corticosterone concentrations have a sex-dependent impact on partner preferences in prairie voles [4]. When males have higher concentrations of corticosterone in the nucleus accumbens, they are more likely to form partner preferences quickly. When females are stressed with high levels of corticosterone, they do not form partner preferences as quickly. These findings show that reductions in HPA axis activity support the development of mate preference in female prairie voles.

Previous sexual experience can also help pair-bond in both sexes of voles. Studies have shown that vasopressin agonists facilitat pair-bonding in sexually experienced male voles.

The vasopressin antagonist is effective at preventing the effects of vasopressin from facilitating pair-bonds in males. Socially naive prairie voles develop preferences for partners from which they receive oxytocin surges, but not vasopressin surges. High specificity oxytocin receptor agonists induce spontaneous and evoked activity depending on social experience in voles [9]. Treatment of vasopressin antagonists does not inhibit a partner preference for the sexually experienced females like it did with the males. This research shows that the way that males and females prefer partners does differ. Oxytocin is important for the formation of a pair bond in female prairie voles, while vasopressin is more important for the formation of a pair-bond in male prairie voles. In order for an animal to form social relationships, it is important for them to have a strong social recognition.

"She's Not Afraid" - One Direction

The amygdala is associated with fear and the septum is associated with love. Amygdala activity decreases when a participant sees their romantic partner, while septal activity is increased [1]. The activation of the amygdala suggests that love reduces the fear response. The septum is a self-stimulatory reward area that involves emotional responses. This could involve relief from negative emotional states or increased pleasure from positive emotional states.

"Addicted to Love" - Florence + the Machiene (Robert Palmer)

The neural mechanisms around romantic love are highly rewarding. Romantic love is initially sparked by visual input, but other elements like voice, intelligence, charisma, and social and financial standing can also be significant [1]. The medial insula, anterior cingu-

late, striatum, hippocampus, and nucleus accumbens are activated when you stare at someone you truly care for.

The "emotional brain" refers to certain areas of the cerebrum. The emotion of love makes people feel excited and euphoric. Neuromodulators help you feel happy, rewarded, and addicted to things you want. Dopamine is the main neuromodulator. Dopamine is responsible for the rewarding properties that drive social contact and relationships. The same circuitry in the emotional brain becomes active when an exogenous opioid drug is used. The monogamous prairie voles' counterparts, polygamous montane and meadow voles, engage with multiple partners over their lifetime [10]. Dopamine may hold the key to understanding this addiction to love for monogamous prairie voles and promiscuity for polygamous voles. There are several dopamine receptor subtypes that are known to play a role in sexual behavior and relationships in both types of voles.

"Soulmate" - Lizzo

Why are these monogamous prairie animals "addicted to love" yet their polygamous counterparts who live in the mountains and meadows engage in lifelong promiscuity? The neurotransmitter dopamine, which has previously been linked to drug addiction, may hold the key to that answer. Dopamine receptor subtypes play a role in both the formation of pair bonds and the maintenance of those relationships. In the socially monogamous prairie vole, dopamine-2 receptors facilitate attraction between mating partners, while dopamine-1 receptor activation maintains the attraction of the newly founded pair bond [6]. As seen in the figure to the right, pair-bonding prairie voles have increased numbers of dopamine-1 receptors. Polygamous montane voles have dopamine-2 receptors and very few dopamine-1 receptors[6].

Positive and negative encounters can also impact how one later perceives, interacts with, and feels about another person during the course of a social relationship. In neuroscience terms, brain systems that engage when relationships are established and expressed are likely to alter over time. Neuromodulators influence social behavior by acting centrally in the brain. One important neuromodulator for controlling social behavior is oxytocin, which is also a target for the therapy of neuropsychiatric illnesses. Neurons in the supraoptic and paraventricular nuclei of the hypothalamus are the primary sources of oxytocin [9]. As relationships develop, oxytocin is produced in the brain, which promotes experience-dependent social adaptations like the development of social memories and mating-induced pair bonds[1],[8]. By altering neuronal activity in the parts of the brain that control social actions, oxytocin has the effect of making social cues more attractive and rewarding. Oxytocin neurons are activated in response to social cues including hugging and hand-holding. These occasions present a chance for oxytocin

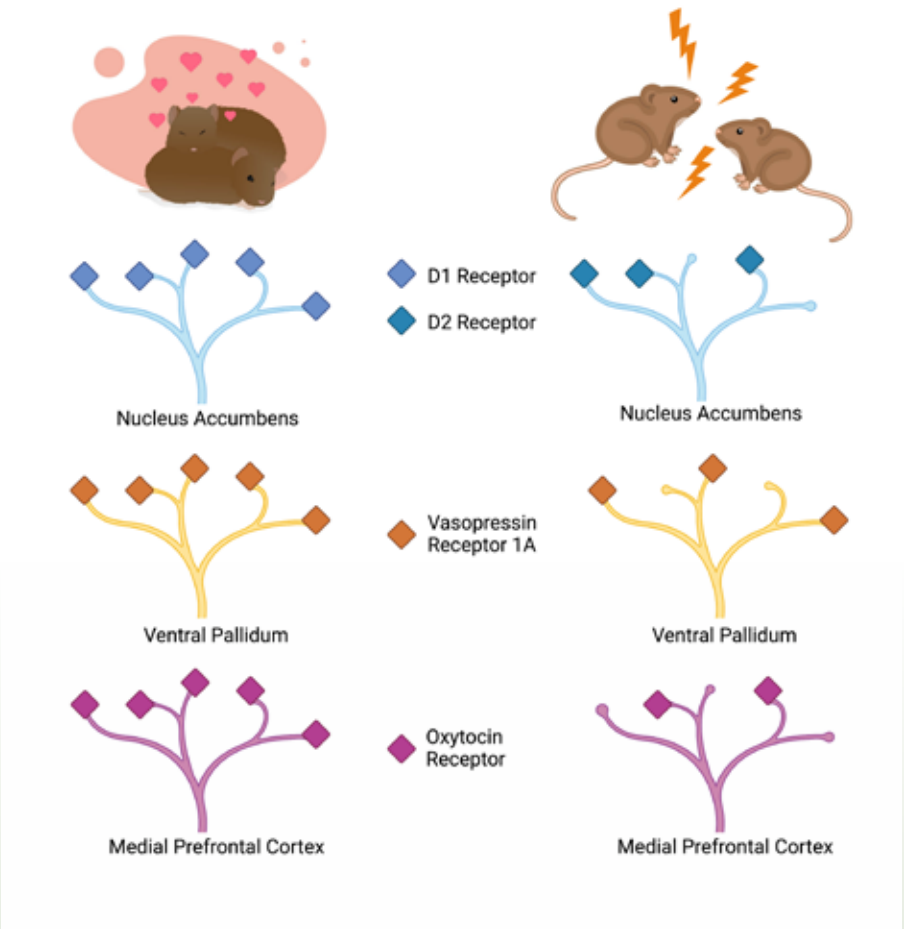

Figure 1. Visual of receptors in Prairie Voles compared to Montane Voles. Created with BioRender.com by Olivia Smith. Figure adapted from: Gobrogge & Wang 2016.

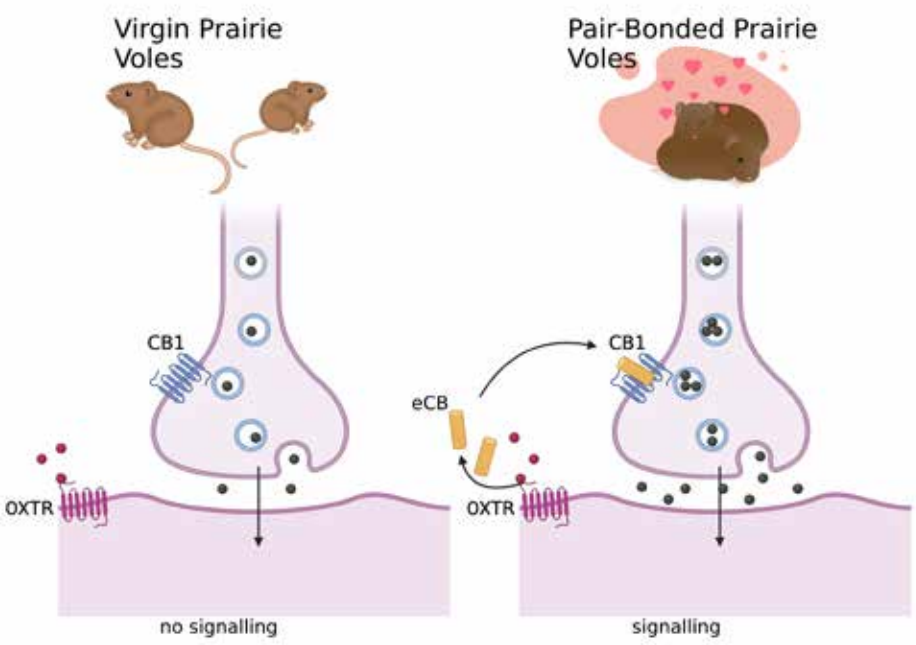

Figure 2. Endocannabinoids facilitate glutaminergic signaling, promoting more excitatory postsynaptic currents. More glutaminergic signaling, more love. Created with BioRender.com by Olivia Smith. Figure adapted from Borie et al. 2022.

to modify the expression of social ties as a relationship progresses.

Pair-bonding is a long-lasting relationship that monogamous prairie voles develop [10]. These behavioral changes brought on by finding their partner and developing a relationship change how they interact with other voles. Their actions are accompanied by parallel changes in the neural dynamics of the brain regions mediating social behavior, more notably the nucleus accumbens, which sits at the meeting point of the social neural network and the mesolimbic reward network. Oxytocin receptors are expressed at higher levels in the nucleus accumbens of monogamous prairie voles and humans compared to non-monogamous animals. The number of oxytocin receptors in the nucleus accumbens is a key factor in the development of an individual preference. The locations of oxytocin receptor densities in monogamous prairie voles are highest in the prelimbic cortex, nucleus accumbens, and amygdala. Oxytocin receptors are not evident in these brain regions of polygamous montane or meadow voles [4].

In order to determine if oxytocin has various physiological effects depending on whether a pair bond is being formed or expressed, the nucleus accumbens activity was modulated by oxytocin in both sexually naïve animals and pair-bonded females. Oxytocin receptor agonists (which stimulate the release of oxytocin) decrease synaptic firings in the nucleus accumbens of virgin animals, which may help couples connect. However, through a connection to an endocannabinoid receptor type 1-dependent, presynaptic mechanism, glutaminergic transmission in pair-bonded females increases [9]. This increases glutaminergic transmission in pair-bonded females. Inhibition of CB1 in vivo suppresses defensive reactions in which the partner is present, thereby assisting in maintaining a trajectory for bonding [9].

Endocannabinoids are defined as the endogenous ligands of cannabinoid receptors (CB1 and CB2) and a growing body of evidence has emerged on the role of the endocannabinoid system in the regulation of several physiological conditions and numerous diseases [11]. Endocannabinoids have recently emerged as an important modulator of emotional and non-emotional behaviors, obviously including one of the most all-consuming emotional behaviors: love. High specificity oxytocin receptor agonist induced potentiation of nucleus accumbens is associated with social preference. Nucleus accumbens oxytocin receptors potentiate excitatory transmission through an endocannabinoid mechanism in paired females. Endocannabinoids are retrograde signaling molecules modulating the synaptic strength between two cells. Endocannabinoids are necessary for the high specificity of oxytocin receptor agonist-induced potentiation observed in paired females. Blocking CB1 receptors in nucleus accumbens of paired females increases partner rejection [9],[11]. Endocannabinoids are the link between the pair-bonded prairie voles that make them stay pairbonded because endocannabinoids promote glutaminergic signaling which increases oxytocin.

"When I Was Your Man"
- Bruno Mars

We are not monogamous prairie voles, unfortunately. We are human and much more affects our love lives. You loved someone and became addicted to them, but you broke up. What now? How has your brain chemistry changed and

what is happening? Yes, your heart is broken, but you are also going through withdrawals. The reward pathway that once was filled with holding hands and hugs is now left empty. What can you fill it with to get over your ex? Alcohol and drugs? Not the best option. Understanding the nitty gritty neurochemistry of love can help people get over past relationships and learn to trust new relationships.

Love can help to reduce the amount of pain you feel. People who look at pictures of someone they love experience a 15% reduction in severe pain and a staggering 40%reduction in moderate pain. Studies have shown that couples who hold hands feel less pain than those who don't. Love is strong and powerful, and it can definitely make a difference in someone's life. A loving relationship can provide significant boosts in both physical and mental health, without the side effects associated with illicit drugs. Love is a drug that can help us feel good during the early stages of a relationship, but it can also cause us pain later on.

Reduced global integration and reduced spatiotemporal variability in the brain is associated with more depressive symptoms, implying a reduced capacity of the brain to regulate and merge the incoming information from distributed regions [12]. This shows evidence of depression changing the brain. Losing someone you love can be hard whether they are gone forever or still alive. It can cause depressive symptoms and feel like physical pain at the same time. The results of this study were found using ignition based measures of integration, hierarchy, and meta stability show a negative correlation between these measures and depressive ratings[12].

"So What?"
- P!nk

And to sum it up, there are song categories for any type of love you may feel. Kesha wasn't lying–your love really is addicting and the prairie vs. montane voles study discussed earlier shows that. Dopamine being released in the mesolimbic pathway reinforces love. Elvis Presely wrote "Can't Help Falling in Love," and he really couldn't. It is basic human nature to fall in love. Lust is the first stage to falling in love and Beyoncé said it best in her song "Bootylicious." Beyoncé also says you're flawless, and she was right! Attraction is such an important stage in falling in love with someone and visuals are what draws people in at first. Along with lust comes sex, so "Let's Talk About Sex." Being in close proximity to a loved one releases oxytocin and dopamine, reinforcing an attachment between the pair. Love, as I'm sure most of us have experienced, whether it be with family members or friends or a significant other has been a "Good Feeling." That is because of the rewarding feeling we get from dopamine being released. One Direction wrote a song about a girl who is supposedly "not afraid" of love. This must be because the activation of her amygdala reduced her fear response when she was in love. Prairie voles are "Addicted to Love," and so are humans. Vole species provide a comparative model for studying social behaviors and the underlying mechanisms. I wish it were as easy for me to find my "Soulmate" as it is for monogamous prairie voles to find theirs. "'So What' now," asks P!nk. Well, I guess most humans experience a lot of relationships. Some last and some don't. "When I Was Your (wo) Man," we were in love and our brains were filled with dopamine, oxytocin, vasopressin, etc., making us very happy together. But in the end, humans are different from voles and there is a lot more that plays into relationships.

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