The Role of Dopamine in the Reward System (with relevance for addiction)

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This review deals with the tasks of dopamine as a neurotransmitter in the central nervous system. Dopamine can transmit its signal via its various receptors and via the four major dopamine pathways out of this four, we will mainly deal with the reward system. It will briefly discuss the original function of the reward system but will also consider further applications and its relevance for addiction.   
 The reward system promotes the survival and reproduction of an organism and a species. Out of initial random movements, an organism develops a goal-oriented behaviour to obtain a pleasant reward. At the core of the reward system lie the ventral tegmental area and the nucleus accumbens. These brain structures are indispensable for all functions related to a motivation, learning and reward-seeking. Dopamine influences these processes also in further brain areas such as the prefrontal cortex and the amygdala where it is involved in different types of fear learning, extinction, associative learning and reversal learning amongst others.   
 Drug addiction can be viewed as a cycle of spiralling dysregulation of the brain reward system that gets stronger after each use of the drug, ultimately resulting in the loss of control in taking abusive drugs. The development of addiction has been associated with several neurocircuitry changes that will be discussed more detailed in this review. All drugs of abuse are supposed to trigger an increased dopamine projection into the nucleus accumbens and thus express their reinforcing effects. Chronic administration of abusive drugs leads to altered dopaminergic pathways, especially the indirect pathway which is mediated through D2R seems to be important in drug seeking.  
 Higher prevalence of obesity in today’s science has led to increasingly more studies that further examined the concept of food addiction in the past years. In this review, we will shortly illustrate the connection between food addiction and the dopaminergic reward system.

*Functions*

Dopamine is a catecholamine that is mainly used as a neurotransmitter in the CNS but does also have some functions in the periphery. In the kidney, dopamine is considered having a promoting effect on natriuresis, it stimulates the exocrine secretion and vasodilatation in the pancreas and increases the blood-flow in the renal mesenteric, coronary and cerebral vessels. (Thorner, 1975)

Despite the effects of dopamine in the periphery in the body of a human, this review is mainly focusing on its relevance as a neurotransmitter in the central nervous system.

Dopaminergic fibers are the most present in four pathways, one of which is the nigro-striatal pathway, were dopaminergic neurons from the substantia nigra in the midbrain connect GABAergic basal ganglions in the dorsal striatum. The degeneration of this pathway leads to Parkinson’s disease and to typical symptoms of motor skills deficiency This reflects the natural functions of this pathway, the control of motor function and learning of new motor skills and his overall role in movement. (Ayano, 2016; Aminoff, 2004)

Dopamine released in the tuberoinfundibular pathway is the main inhibitor of the prolactin secretion in the anterior pituitary gland. Dopamine is produced in the arcuate nucleus of the hypothalamus and is transported to the median eminence, where it gets released into the blood vessels, which supply the pituitary gland. Dopamine then acts on lactotrophic cells that produce prolactin. The blockage of dopamine receptors by antipsychotic drugs results into an increase in milk production and secretion (galactorrhea).(Ayano, 2016)

The mesocortical pathway refers to dopaminergic neurons of the ventral tegmental area that project to the frontal cortex and septohippocampal regions. These projections are thought to be involved in cognitive and emotional behaviour. Distinct levels of dopamine in the frontal cortex help in improved working memory and attention, but changes in the dopamine levels to either side can lead to memory impairment. This pathway could correlate with the negative symptoms of schizophrenia, when impaired. (Ayano, 2016)

The mesolimbic pathway is intricately linked to the reward system as dopamine forms the chemical basis of the experience of pleasure and its repeated hunt for more. The dopaminergic fibers originate in the ventral tegmental area in the midbrain and project to the amygdala, pyriform cortex, lateral septal nuclei and the nucleus accumbens. Dopamine is released after pleasurable situations and rewards the person for this activity, which stimulates one to seek out this activity more often. The same process applies to the abuse of drugs, which activates the dopamine release in the mesolimbic system. (Ayano, 2016)

The mesocortical and mesolimbic systems overlap in terms of their behavioural outcome and have similar functions. Therefore, they are collectively called the mesocorticolimbic system.

*Synthesis*

As it is common for catecholamines, the synthesis of dopamine begins in the liver with the production of the amino acid tyrosine out of the essential amino acid phenylalanine with the aid of the enzyme phenylalanine hydroxylase. Tyrosine is transported out of the liver to the catecholaminergic neurons in the ventral tegmental area of the substantia nigra in the midbrain and the arcuate nucleus of the hypothalamus for further processing. The enzyme tyrosine hydroxylase accelerates the attachment of a hydroxy group to tyrosine, this time-limiting reaction leads to L-Dopa, which is the last intermediate product that could pass the blood brain barrier, as dopamine itself is not capable of doing that. Dopa decarboxylase converts L-Dopa quickly into dopamine, which could now be further processed into noradrenaline and finally adrenaline. Dopamine is an intermediate product of the biosynthesis of adrenaline but has its own independent functions as a neurotransmitter.

*Receptors*

Dopamine carries out its functions by activating five dopamine receptors, D1, D2, D3, D4 and D5. They all belong to the large G-protein coupled receptor family and therefore have the typical 7 transmembrane domain structure. These five distinct dopamine receptors are further subdivided by their structures into the D1-like group, that consist of the D1 and D5 receptor and the D2-like group were D2, D3 and D4 belong to. The D1-like group has a larger structural homology than the D2-like group. D1 and D5 are to 50% structural identical, this is reflected in their similar affinities to a variety of dopaminergic drugs. The activation of the D1-like group by dopamine occurs via the opening of sodium channels, which is an excitatory response, or on the other hand, via the opening of potassium channels, which results into an inhibitory response. The D2-like activation leads usually to an inhibition of the target neurons (Arias-Carrián et al, 2010; Ayano, 2016) **.**

The final effect that dopamine has on his target neurons depends on which receptors are expressed and what the internal responses to the activation is. The five dopamine receptors are not equally spread in a human’s body and do all have slightly different outcomes:

The D1 receptor is the most abundant in a human nervous system and is found in high concentrations in the mesolimbic, nigrostriatal and mesocortical areas of the brain, such as the nucleus accumbens and the striatum. After knowing its preferential locations, it is not surprising that the D1 receptor is needed for voluntary movement, attention, reward, working memory and learning. Outside its functions in the central nervous system, dopamine is also known to modulate the renin levels in the kidney (Ayano, 2016).

The D2 receptor is the second most abundant receptor and is found in fairly similar brain areas. It is needed for regulating mood and emotional stability in the limbic system or movement control in the basal ganglia. The D2 receptor is especially important in terms of drug abuse and as main receptor for most antipsychotic drugs. In the periphery, the D2 receptor is present in blood vessels and can lead to vasodilation and changes in blood-pressure (Ayano, 2016).

The D3 receptor is exclusively found in the central nervous system and is mainly involved in emotion control (Ayano, 2016). The D4 receptor is expressed in the hippocampus, amygdala, thalamus and in the hypothalamus, but it has the lowest presence of all five dopamine receptors. Its central role is the modulation of cognitive functions. The D4 receptor was also found to regulate the renal function, gastrointestinal motility, vasodilation and blood pressure (Ayano, 2016). Processing of painful stimuli and regulation of the endocrine functions of dopamine are both controlled via the D5 dopamine receptor (Ayano, 2016).

The final effect dopamine has on its target neurons is depending on the concentrations of the different dopamine receptors, that are expressed, and can therefore have a large variety of outcomes (Arias-Carrion et al, 2010).

*The reward system and its functions*

The survival of a species depends on its ability to achieve the highest fitness in a particular environment Over time, only those organisms that were best able to reproduce, will prove to be superior under the forces of natural selection. But how does a certain organism know whether it is performing an evolutionarily beneficial action or not? This is the key role of the reward system, it fulfils its purpose by creating in all living organisms the desire to do actions that lead them to stay alive longer and reproduce. A species succeeds in natural selection, when it has the most advantages over another species in a given environment. To promote the best survival and reproduction strategies, the brain has evolved a reward system in order to learn, select and approach the best objectives and situations appropriate for an individual’s survival. Rewards have been adopted by the brain to tackle the challenges of evolution (Schultz, 2015). But what are rewards actually inducing and how can they help an individual to be the fittest? Rewards induce mainly the following three things:

*Learning*

Rewards are positive stimuli that are pleasurable and nice to encounter, they let the organism learn, which behaviour makes them feel good. This leads organisms to seek them more often. The rewards act as a positive reinforcer and increase the frequency of behaviour that leads to them. Rewarding stimuli can be learned with operant and classical conditioning (Arrias-Carrion et al, 2010; Schultz, 2015).

*Approach behaviour and decision making*

To get a mating partner or food we have to approach the object of interest. Rewards help an organism to approach more often and more confidently. There are different kinds of rewards and they induce all different combinations of feelings and emotions. Some of them we like more, others we do not like that much. We do want to get those rewards that are the most pleasurable for us and therefore we are going to make more and more decisions that help us get the desired rewards (Schultz, 2015).

*Pleasure*

Pleasure is an emotion that is wonderful to feel but it is only a passive experience from a reward. After a while of enjoying pleasure, we have the desire to feel this emotion even more often. Desire is an emotion that makes a behaviour purposeful and directs it towards a goal, which means that desire is an inner force that actively directs behaviour. Pleasure and desire make us perform actions that we perhaps would not consider doing without knowing in beforehand that we get a reward in the end (Arrias-Carrion et al, 2010; Schultz, 2015).

By definition, rewards have no physical properties. Instead, they are defined by the behavioural reactions they induce in an organism. Since rewards have no physical properties, no organism has specialized sensory receptors for it like for hearing, somatosensory or visual stimuli. This fact adds another level of difficulty for researchers to study reward-related behaviour, because behavioural responses are one of only few things that can be detected and investigated. But there may be a good reason why no such receptors exist. It may be much more efficient to have a neuronal system that filters out the reward components. There is a great variety of objects that could partially induce a reward, these impressions are taken up by already existing sensory receptors. The reward system combines all the different sensory inputs to one pleasurable outcome. But how does this neuronal pathway look like? (Schultz, 2015)

*Anatomy of the reward system*



**Figure 1 |**  *Projections of dopaminergic neurons in the reward system, Ventral tegmental area (VTA), Substantia nigra compacta (SNc), (Arias-Carrián et al., 2010).*

The mesocortical and mesolimbic pathways mentioned above are suggested to contribute the most to control and to the regulation of emotion-related behaviour. The mesolimbic system includes the ventral tegmental area (VTA), that plays a crucial role in learning processes. The dopaminergic neurons of the VTA project to the nucleus accumbens. The mesocortical system connects the VTA to the prefrontal cortex. Other brain areas such as the amygdala, substantia nigra, hippocampus and hypothalamus are also thought to be involved in the reward system. The dopaminergic neurons act on either D1-like receptors or D2-like receptors to either stimulate (D1-like receptors) or to inhibit (D2-like receptors) the production of cAMP as second messenger. Dopamine is not the only neurotransmitter to play a role in the reward system, but also glutamatergic interneurons and GABAergic medium spiny neurons are present in the reward system and contribute their part to it. (Björklund & Dunnett, 2007)

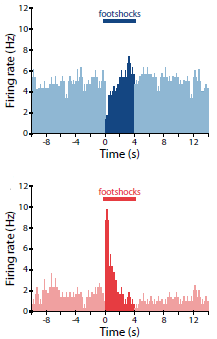
**The functions of dopamine in motivation, learning and the reward system**

Since time immemorial, animals have been seeking rewarding stimuli as it results into pleasurable sensations. In the animal kingdom, the search for rewards, such as water, food and sex amongst others, is tightly linked to survival of an individual and the species as a whole. Stimuli that lead to such actions are intrinsic or unconditioned stimuli (US). These stimuli lead to a naturally occurring pleasurable response, also known as unconditioned response (UR). They are intrinsically present, while other stimuli have to be learnt first to result into a reward. We call these extrinsic or conditioned stimuli (CS) that result into a positive or negative outcome (CR) (Bouton, 2007). For an organism to form this connection, a CS normally co-occurs with a US during a training phase. Scientifically speaking, reward-seeking induces specific behaviours in an organism. We can thus discern different functions for reward-seeking.

Dopamine has been long implicated in motivation, learning and reward-seeking (Abraham et al., 2014; Ranaldi et al., 2014; Saddoris et al., 2015). These behavioural processes are intimately linked to one another and different brain areas have been shown to play a vital role in these processes. To further add to the complexity of the system, other pathways overlap with the dopaminergic system such as the serotonergic, cholinergic, GABAergic, orexinergic and noradrenergic system (Hrabovszky et al., 2013; Wise et al., 2010; Chuhma et al., 2014). The interaction of anatomically distinct brain areas in the dopaminergic system give rise to different types of learning stages and motivation (Saddoris et al., 2015).

*Ventral tegmental area and reward prediction error*

The ventral tegmental area (VTA) is a key area in the mesocorticolimbic dopamine system. The VTA receives inputs from various brain areas (Morales et al., 2017) and its dopamine neurons project to several other brain structures involved in motivation and learning such as the nucleus accumbens core, shell and the prefrontal cortex. The VTA shows strong dopaminergic activity during reward-related learning in form of phasic DA impulses (Schulz et al., 1997). In the pioneer study from Schulz and colleagues (1997), it was shown that there was a significant increase in the dopamine levels in the VTA of the monkey brain when performing a learning task upon consumption of a reward initially. After the training phase, phasic dopamine impulses were already observed upon presentation of the first environmental cue (appearance of light that indicated to press the lever to obtain a reward), but the initial phasic dopamine impulses diminished upon reward consumption. On the other hand, the knockout of dopamine signalling in the VTA and NAc (knockout of D2 receptors) has been shown to impair aversive learning and is therefore a necessary prerequisite for it (Danjo et al., 2014)**.**  
These phasic dopamine impulses correlate strongly with reward-seeking behaviour and learning. It is generally said that this DA neuron pulsing encodes a so-called “reward prediction error” (RPE). The RPE is the actual value of a rewarding stimulus minus the expectancy of the value of a rewarding stimulus. Therefore, the RPE can be distinguished in positive RPE, neutral RPE or negative RPE. A positive RPE indicates that the final reward was more pleasurable than initially expected, which generally leads to learning, such that the environmental cues leading to that reward are identified (Saddoris et al., 2015). A positive RPE can also originate from a surprising positive reward. A neutral RPE indicates that the expected pleasurable sensation of a reward was the same as the actual outcome. In the case of a negative RPE, the reward was disappointing so to say, that is, the result was less satisfactory (Arias-Carrión et al., 2007). A negative RPE induces aversive learning in order to avoid future unpleasant or painful situations (Abraham et al., 2014). Dorsal dopaminergic neurons in the VTA usually show a decrease in the firing rate to noxious stimuli (foot shock), while an increase in activity can be observed in ventral dopaminergic neurons in the VTA (fig. 2) (Brischoux et al, 2009).

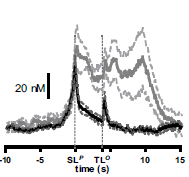


**Figure 2 |** *Adapted from Brischoux et al. (2009). A foot shock to the hind paw of anaesthetized rats was applied and DA neurons activity in the dorsal and ventral VTA was recorded. In the upper figure, we see an initial decrease in DA neuron firing in the dorsal VTA. A noxious stimulus inhibits that neural activity. In the lower figure, there is a sharp initial increase in DA neuron firing in the dorsal VTA. These neurons are excited by a noxious stimulus.*

Dopamine is not the only neurotransmitter acting in the mesolimbic pathway. The mesolimbic dopamine pathway has been shown to be subject to cholinergic modulation (Mark et al., 2011) and transient receptor potential vanilloid 3 in the VTA (Singh et al., 2016).

*Dopamine in the Nucleus Accumbens Core and Shell*

The Nucleus accumbens (NAc) is part of the mesolimbic pathway and receives inputs from the VTA. It is important to discern that the NAc core and NAc shell compute neural inputs for different kinds of learning (Saddoris et al., 2015). The NAc core also performs RPE computation while the NAc shell is involved in incentive salience (Saddoris et al., 2015). This can be a source of confusion, since it seems that the NAc shell activity usually shows a high activity in incentive salience, while the NAc core is best studied with reward-related theories, though it is also active in incentive salience (fig. 3) (Saddoris et al. 2015).



**Figure 3 |** *Adapted from Saddoris et al. (2015). Measurements of the Nucleus accumbens core are represented by the bold black line, measurements of the Nucleus accumbens shell are represented by the bold grey line. DA neuron signalling was measured in the Nucleus accumbens core and shell in mice during a lever-press task. Peak values are reached when pressing the first lever (SLp) in core and shell. As the mouse proceeds with the task, the dopamine levels in the core fall quickly to baseline levels (with a smaller increase during the press of the second lever (TL0)), while dopamine signalling in the shell remains constantly high exemplifying its relevance in incentive salience. At the end of the task, dopamine signalling returned to the baseline.*

*Dopamine in fear learning and extinction*

The amygdala is an indispensable component in fear learning and required in the consolidation of memories associated with fear. It is also part of the mesolimbic pathway, since VTA projects to the amygdala. Proper memory establishment also involves further brain structures such as the hippocampus and the NAc.

Fear conditioning is a very fast process where a CS is paired with a shock that acts as an US. For example, a sound (CS) occurs at the same time as a foot shock (US). The mice will show an aversive response to the foot shock, but initially, the sound will not induce a remarkable behaviour in a mouse. After the training phase, the mouse will have made a connection between the sound and the foot shock (the sound predicts the foot shock), which will be enough to induce a fear response. The process of fear extinction describes the behavioural change of an animal to a CS, where no fear response is the outcome. This does not mean that the initial fear memory has been deleted, but that the animal has adapted to its environmental situation (the RPE of the CS has become neutral) (Abraham et al., 2014). Much of the current research has been especially focused on D1 and D2 receptors. D1 receptors result into an excitatory response, while D2 receptors result into an inhibitory response (Arias-Carrián et al, 2010; Ayano, 2016). Selective knockout of D1 receptors with antagonists have shown that such mice have impaired fear acquisition. Knockout of D2 receptor in mice lead to controversial results. Mueller and colleagues report an impairment in fear extinction retention (Mueller et al., 2010) while Ponnusamy and colleagues report enhanced fear extinction using D2 receptor antagonism (Ponnusamy et al., 2005). Differences in results were proposed to be due to the affinities of used antagonists and slight differences in task protocols (Abraham et al., 2014).

*Dopamine in associative learning*

The prefrontal cortex has been linked to a multitude of higher-order functions, such as attention, planning, evaluation, decision-making, executive functions and many more cognitive functions (Funahashi et al., 2013, 2017). Unsurprisingly, it is also a key component in associative learning (Puig et al., 2014) as learning new associations of the environment increases the organism’s adaptability and survival.

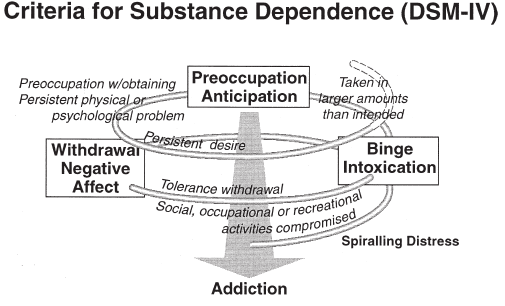
The PFC receives dopaminergic projections from the VTA during a learning task (Puig et al. 2014). PFC dopaminergic neurons show a phasic spiking behaviour, albeit it is less frequent and slower than in the VTA or NAc core, indicating that the PFC dopamine release is involved in RPE. It has been proposed that these dopamine spikes are correlated to looking for more abstract rules regarding the conditions a reward occurred (Puig et al. 2014). Furthermore, the PFC-BG loop is only involved in the early stages of learning. As soon as a habit has been formed, the PFC is not involved in the reward-seeking behaviour of an organism (Puig et al. 2014). Depletion of dopamine in the orbitofrontal cortex have shown to have no effect in reversal learning (the ability of an organism to learn that a previously CS leads to no positive reward anymore, but results into no reward at all) (Puig et al. 2014). Reversal learning in the orbitofrontal cortex is heavily influenced by the serotonin, which is why dopamine depletion did not affect reversal learning in any major way (Puig et al. 2014). Thus, the role of dopamine in the PFC has yet to be elucidated with regard to how dopamine influences these processes and to what extent other systems, like the serotonergic system, overlap with the dopamine system.

**Drug Addiction**

Drug addiction is a recurring relapse disorder that can be characterized by three major characteristics, by (1) compulsion to take the drug, (2) loss of control and thus excessive drug intake, (3) a negative emotional state which is usually caused by withdrawal of the drug (Koob et al.,2010).

Drug addiction is not a static episode and can be very well represented by an increasing addiction cycle (Baumeister et al. 1994). The psychiatric addiction cycle consists of three major factors: Binge-intoxication, withdrawal-negative effects and preoccupation/anticipation (Koob and Le Moal, 1997). Spiraling distress acts as the reason to why an early self-regulation failure can be the cause of emotional distress and therefore be the reason to set the cycle in motion. Spiraling distress can also be defined as the gradual disruption of the dopamine reward system within the context of reoccurring addiction cycles.

It is also important to mention that the addiction cycle contains the idea of a constant play of positive and negative reinforcements. In which positive reinforcement can often be described as the satisfying effects, induced by drug use, in the absence of any negative emotions. Whereas negative reinforcement is associated with an alleviation of a negative state for example caused by drug withdrawal (Wikler, 1973). Positive reinforcement relates mostly to the binge intoxication state in the addiction cycle and negative reinforcement is related to the withdrawal negative-affect state. Conditioned positive and negative reinforcement occurs by pairing a neutral cue with an acute positive effect of a drug, whereas those are related to the preoccupation/anticipation stage. The three stages of the addiction cycle therefore interact with each other and become worse the longer this cycle goes on, which in the end leads to what one understands as drug addiction (Koob and Le Moal, 1997).

 The shift from recreational drug use to addiction is based on the change of several neurocircuitry pathways, one of the most important ones being the mesolimbic dopamine pathway, which will be discussed in more detail later in this review.

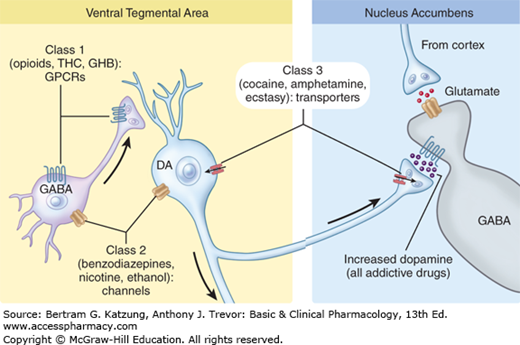
**Figure 4 |** This figure depicts the idea of a spiraling addiction cycle. Containing the three major components: Binge intoxication, withdrawal negative-effect and preoccupation anticipation. The basic idea of this diagram is to show that each cycle in this spiral will add up and ultimately lead to addiction (Diagnostic and Statistical Manual of Mental Disorders, 4th edition).

*Classification of Drugs*

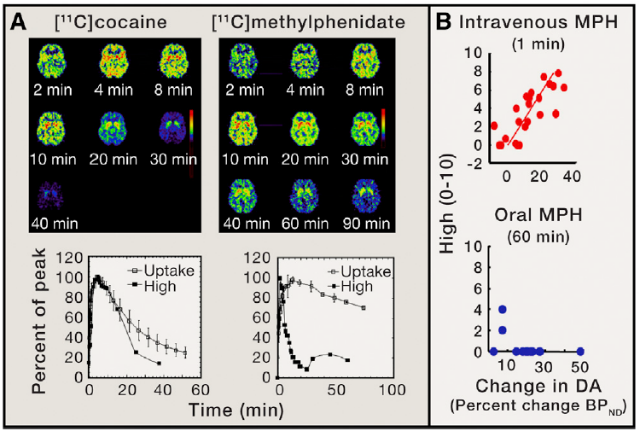
Most known drugs of abuse, for example alcohol, cocaine, marijuana etc. act on elements which are part of the limbic circuitry and thus lead to upregulation of dopaminergic projections from the ventral tegmental area into the nucleus accumbens (Purves et al., 6th edition).

These drugs can be categorized into three different groups (Figure 5), depending on how they achieve increased dopamine projection (Nugent et al, 2007). Class 1 contains drugs such as opioids or ∆-9-Tetrahydrocannabinol (THC). These usually bind to G protein-coupled receptors and act as an agonist on these receptors which are found in GABA inhibitory interneurons. Binding to the GPCRs leads to disinhibition of dopaminergic neurons in the ventral tegmental area (Lüscher and Ungless, 2006). Drugs like nicotine or ethanol, that are consumed by a large part of todays society, belong to the second class. These drugs act on the channels located on

GABA inhibitory interneurons or dopaminergic neurons in the ventral tegmental area. Class three drugs on the other hand can act in both the ventral tegmental area and the nucleus accumbens. These drugs inhibit the reuptake of neurotransmitters such as dopamine, e.g. cocaine or ecstasy inhibit the monoamine transporters which are responsible for reuptake of dopamine and therefore lead to a stronger dopaminergic signal in the nucleus accumbens (Katzung et al, 13th edition).

As one can see, all the prominent abusive drugs lead to a higher dopaminergic signal in the nucleus accumbens in one way or another and thus directly trigger the dopamine reward system. This effect seems to play a fundamental role in the process which leads to drug addiction, because of the earlier mentioned neuroplasticity changes which are ****caused by disruption of the reward system.

**Figure 5 |** *Shows a DA neuron in the VTA that projects into the NAc, DA neuron is shown to be inhibited by GABA neuron. Three classes of abusive drugs are shown that all lead to increased DA in the NAc. Class one and two only act in the VTA whereas class three drugs act in VTA and NAc.*

*DA signaling*

The ventral striatal direct and indirect pathways both play an important role in DA signaling induced by drug reward. Previous studies showed an association of the direct pathway with reward. On the contrary the indirect pathway is associated with punishment (Hikida et al., 2010; Kravitz et al., 2012). Therefore, increased binding of DA to D1R leads to a reward response, whereas binding to D2R mediates aversive responses of the reward system.

Experiments showed that activation of the indirect pathway is mandatory to produce drug reward, contrary to the activation of the indirect pathway on its own which does not lead to any drug reward (Caine et al., 2007; Caine et al. 2002; Durieux et al., 2009; Norman et al., 2011). Activation of both pathways leads to the biggest drug reward (Steinberg et al., 2014; Welter et al., 2007). Additionally, D2R show low affinity towards DA compared to D1R. This further means that DA increases need to be fast and specifically large enough to activate D1R receptors, so that the direct pathway will be activated and the indirect pathway will be inhibited. Further experiments confirmed that drugs which cause fast increases in DA lead to an increased drug “high” in comparison with drugs that lead to a slower and smaller DA increase (Volkow et al., 2008). More precisely, large DA increases by drugs over a short amount of time (< 10 min) were associated with the drug “high” whereas DA increases over a larger amount of time (> 60 min) showed barely an effect in terms of drug “high” and therefore suggesting no specific drug reward (Figure 6). All those observations lead us to the conclusion that a fast and big enough DA increase is necessary to activate both pathways and achieve the best drug reward signaling. Moreover, it may also explain why the way of consummation might be of great importance in regard of addiction, because faster routes of administration like intravenous injections lead to a bigger and faster DA peak, compared to slow routes of administration such as oral consumption (Volkow et al., 2015).

**Figure 6 |** *(A) Shows pharmacokinetics of cocaine and methylphenidate. On the top, axial brain images after intravenous drug uptake at different times are shown. On the bottom, time activity curves of both drugs are depicted in combination with drug “high”. This figure suggests that the “high” is directly associated with the rate of DA increases.*

*(B) Linear regression between drug “high” and methylphenidate induced DA increase is plotted, comparing intravenous vs. oral route of administration. Clearly shows that oral way of consumption barely leads to a “high”, because of the slow brain uptake. (Volkow et al., 2015)*

*Reward prediction error and addiction*

Since reward prediction error (RPE) has already been discussed in this review in a more general matter, we will now focus on how it is related to addiction and may be fundamental to cause addiction or lead to relapse. To shortly summarize prior knowledge about RPE, it can be described as the difference between what was predicted and what was received. The RPE is said to be positive if what was received is bigger than what was predicted and the RPE is negative if what was predicted was bigger than what was received (Purves et al., 6th edition).

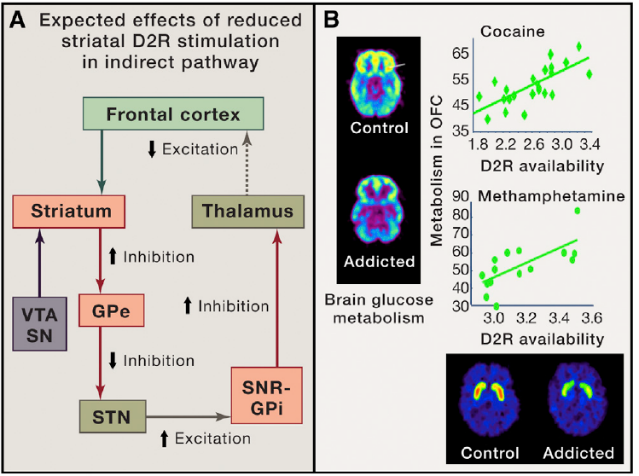
Drug consumption that leads to big enough DA increases, as discussed in the previous part, are sufficient to activate D1R which can then lead to associative learning also known as conditioning which is crucial for RPE (Zweifel et al., 2009). Cues that are associated with drug consumption can become conditioned after a certain amount of training time, after sufficient training time those cues that are associated with drug consumption can then trigger DA neuronal firing in the VTA which then leads to big enough DA increases in the NAc. The RPE theory basically states that those DA increases coupled to associated cues mirror the expectation of receiving a reward.

If we now look at a natural reinforcer such as food, the RPE will be balanced out after extended training, which means that the DA cells will stop firing after food consumption (Schultz et al., 1997). On the contrary there will be a positive RPE after drug consumption, due to the chemical properties of abusive drugs which promote DA increase in the NAc. This now positive RPE leads to what is known as craving, more precisely the desire to take the drug also during its consumption and therefore leading to an ongoing motivation to keep consuming the drug (Volkow et al., 2015). In other words, drug consumption leads to a linear increasingly cue value because of the positive RPE which is caused by the pharmacological properties of abusive drugs.

*Drug induced Neuroplasticity*

Strengthening or weakening of synaptic connectivity was confirmed to be caused by large enough drug-induced DA increases (Grueter et al., 2012). It is being hypothesized that such neuroplastic changes are based on several changes in epigenetic enhancing/silencing of gene expression and on epitranscriptomic modulation of translation (Kenny, 2014; Robison et al., 2011, Satterlee et al., 2014). Drug induced neuroplasticity induces the same mechanisms that are responsible for learning and memory. Long term potentiation (LTP) is associated with larger synapses and dendritic spines, whereas long term depression (LTD) is linked to smaller synapses and dendritic spines (De Roo et al., 2008). These mechanisms are therefore responsible for creating a long-lasting molecular memory for drug rewarding and conditioning effects (Hyman et al. ,2005). Synaptic strength can be regulated through addition or removal of AMPAR or NMDAR, as well as changes in the subunit compositions of AMPAR. Alteration of AMPAR further leads to increased responsiveness of medium spiny neurons to glutamate in the NAc. To summarize, the increased AMPAR/NMDAR ratio in the VTA leads to further neuroplasticity changes, after repeated exposure, and may in the end lead to behavioral consequences such as relapse to drug seeking (Volkow et al., 2015).

*D2R and addiction*

Several studies have described a downregulated expression of D2R in the striatum after chronic drug administration. Low expression of D2R in the striatum of rodents are also related to escalating and compulsive administration of cocaine (Everitt et al., 2008). Similar results were found in human brain imaging studies for most of the drugs, except marijuana (Volkow and Baler, 2014). As previously mentioned D2R binding is responsible for inhibition of the indirect pathway. Reduced expression of D2R will then end up in reduced inhibition of the indirect pathway. This will lead to reduced excitation of prefrontal cortex (PFC) areas (Figure 7) (Black et al., 2010). Of major importance are the anterior cingulate cortex (ACC) and orbitofrontal cortex (OFC) which are located in the PFC. Those two areas are necessary for self-control and for processing salience attribution, their disruption has been associated with a tendency for impulsive and compulsive behaviors (Volkow and Fowler, 2000). Therefore, reduced D2R expression might enhance the risk for compulsive drug seeking behavior and thus resemble an important cause that leads to drug addiction. Studies in rodents showed results in favor of this hypothesis, in which optogenetic stimulation of the PFC prevented cocaine relapse (Chen et al., 2013).

**Figure 7 |** *(A) Schematic overview of the indirect DA pathway. DA neurons from ventral tegmental area (VTA) and substantia nigra compacta (SNc) project DA signaling into striatal GABA neurons expressing D2R. These striatal neurons then target GABA cells in the globus pallidum external (GPe), which inhibits glutamatergic neurons in the subthalamic nucleus (STN). STN glutamatergic neurons further excite GABA neurons in the substantia nigra reticulata (SNr) and the globus pallidum internal (GPi), those two structures inhibit glutamate neurons in the thalamus which innervates the frontal cortex. Reduced expression of D2R in the striatum therefore leads to impairment of the indirect pathway, resulting in the reduced excitation of the frontal cortex*

*(B) Shows brain glucose metabolism of control and addicted individual, both tested with [11C]racloperide and FDG. On the right side correlation between D2R availability and metabolism in the OFC region is depicted, once with cocaine on the top and below with methylamphetamine. Positive slopes show us the correlation of D2R availability and OFC brain metabolism. (Volkow et al., 2015)*

*Dopamine and food addiction*

Since obesity has become a very important topic in recent years, several studies tried to explain how an individual develops food addiction and in what way it might be connected with the reward system, especially the neurotransmitter DA. Recent studies suggest strong evidence that similar to drug addiction, food addiction involves the dopaminergic reward circuitry of the brain. We will in this review shortly present the concept of food addiction and results of recent experiments.

*Dopamine signaling in food reward*

As we previously discussed in this review, drugs of abuse such as cocaine can alter the dopaminergic mesolimbic system. Several experiments have also shown that palatable food can activate this DA reward circuitry, therefore we can conclude that food addiction has to act in a similar way to drug addiction, in a way that both depend on dopaminergic circuits. Additionally, brain imaging studies have shown that dopaminergic circuits most certainly play a role in the control of food intake (Wang et al., 2001; Small et al., 2001; Volkow et al., 2011).

Comparable to drugs of abuse, studies have shown that rewarding of food stimulates dopaminergic transmission from the VTA into the NAc. Roitman and colleagues have also shown that a cue associated with food reward lead to a DA increase in the NAc (Roitman et al., 2004). Therefore, indicating that DA signaling in the NAc acts as a real-time modulator of food-seeking behavior. However, various other studies have shown that the dorsal striatum is of major importance in regard of food addiction. Especially in humans the dorsal striatum was found to possess a correlation with feeding behaviors. Small and colleagues used positron emission tomography (PET) to reveal that feeding-induced dopamine release in dorsal striatum correlates with meal pleasantness ratings in humans rather than NAc (Small et al., 2003). Additional to these findings, reduced striatal D2R expression has been found in obese individuals in proportion to their body mass index, similar to the scenario that occurred in drug addicted individuals (Wang et al., 2001). This might suggest that DA deficiency may lead to overeating in such a way that eating too much food may compensate for decreased activation of dopaminergic reward circuits. Another possible explanation could be that reduced D2R expression may lead to changes in behavior that lead to addiction, in a similar way to what we already discussed in addiction caused by abusive drugs. Volkow and coworkers revealed a significant association between D2R expression levels and cingulate gyrus (CG), dorsolateral prefrontal cortex (DLPFC) and orbitofrontal cortex. Those areas are involved in inhibitory control, salience attribution and emotional reactivity, which means that disruption of those regions can lead to impulsive and compulsive behaviors (Volkow et al., 2008).

*Conclusion*

A detailed understanding about the neural mechanisms result into reward-oriented behaviour is of paramount importance if one desires to comprehend disturbed forms of reward-seeking such as craving and addiction. In this review, we have presented the VTA and the NAc as the two major areas involved in learning, reward and addiction. Dopamine, but also many other neurotransmitters, contribute to complex processes, sometimes in a redundant manner. The dopamine system does not act purely on its own during a learning task, but is modulated by other systems and works along with the serotonin system, for example in the prefrontal cortex, during reversal learning. Thus, the exact functions of dopamine in many brain areas have yet to be elucidated.

During the last decades, various studies have been done to figure out the causes of addiction and the mechanisms behind it. Dopamine circuits were found to be of major importance and promising hypotheses were proposed. One of the most prominent one being the reward prediction thesis, which also very well explains how the reward system might lead to addiction after chronic drug reward. In addition, several studies have indicated a connection between D2R and neurocircuitry changes. This seems to be a promising approach for further studies, because there are still some controversies that need to be solved. All in all, one can say that better understanding of the dopamine reward system might be very useful to further the understanding of drug addiction.

Experiments have shown the importance of the DA system in terms of controlling eating behavior, especially the D2R is of great importance in food reward. Furthermore, several similarities between addictive drug behavior and food addiction have been observed. Those findings provide a solid foundation for further research that will have to be carried out in direction of food addiction.

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