Bidirectional role of dopamine in learning and memory-active forgetting

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Abstract

Dopaminergic neurons projecting from the Substantia Nigra to the Striatum play a critical role in motor functions while dopaminergic neurons originating in the Ventral Tegmental Area (VTA) and projecting to the Nucleus Accumbens, Hippocampus and other cortical structures regulate rewarding learning. While VTA mainly consists of dopaminergic neurons, excitatory (glutamate) and inhibitory (GABA) VTA-neurons have also been described: these neurons may also modulate and contribute to shape the final dopaminergic response, which is critical for memory formation. However, given the large amount of information that is handled daily by our brain, it is essential that irrelevant information be deleted.

Recently, apart from the well-established role of dopamine (DA) in learning, it has been shown that DA plays a critical role in the intrinsic active forgetting mechanisms that control storage information, contributing to the deletion of a consolidated memory. These new insights may be instrumental to identify therapies for those disorders that involve memory alterations.

Key words: Dopamine, Memory formation, Active forgetting, Aversive memories, Appetitive memories.

1. Introduction

The human being, as well as the rest of the animals, constantly receives stimuli from the surrounding environment. For many years, much attention has been focused on how different environments may influence and alter behavior. Part of what we learn through our lifetime relies on how we acquire, integrate and process new information in a way that makes it available in case of demand. For instance, when a stimulus is capable of generating an aversive response (i.e. a food that turns out to be poisonous, a predator's presence in a given place or some signal of danger), our brain is able to codify and store this information making sure that such experiences will not be repeated (or happen again) in the future. Conversely, when we learn that a natural rewarding stimulus, such as food or sex, generates pleasure, then we are stimulated to try those pleasant sensations again. In addition, as it is widely known, the brain rewarding system can be also activated by drugs of abuse, which interestingly act on the same mechanisms set in motion by natural, pleasuring stimuli (Blanco-Gandía et al., 2020; Lindgren et al., 2018). Moreover, it is important to remark that, when the pursuit of pleasure becomes repetitive and uncontrolled, it could result in maladaptive responses such as addiction. Classical conditioning experiments in which associations can be made between different stimulus were studied by Ivan Pavlov (also known as Pavlovian learning) and were crucial to highlight the critical role of associative learning in the reinforcing effects of drugs of abuse. In his stimulus-response model, Pavlov first described that an unconditioned stimulus (e.g. substances of abuse) that generates an unconditioned automatic response (e.g. the rewarding effects of these substances) could be associated with a formerly neutral stimulus (like a neutral place) such that, eventually, once this association was made, the neutral stimulus (the solely experience of being in that place) could trigger the automatic response (e.g. the drug-seeking behavior). This observation settled the basis of the so-called conditioned place preference (CPP), a widely known behavioral task widely used to study appetitive and aversive stimuli-associations. Of note, a variation of these associations that is extremely useful to study conditioned responses can also be made using an instrumental response. In this case,

for example, animals might be trained to do something (e.g. push a lever) when a neutral stimulus is present in the cage (e.g. a light) and consequently they get a reward (a pellet food).

In this sense, it is crucial that our brain let us remember those positive-rewarded stimuli, but it is equally important that this be done in a controlled manner: accordingly, it is critical to understand how our ability to store information functions in order to keep only those that are actually relevant and erase, through forgetting mechanisms, what it is not (Davis & Zhong, 2017; Frankland et al., 2013). When it comes to forgetting, it is essential to distinguish forgetting from amnesia, since forgetting involves normal physiological mechanisms while amnesia is indicative of a pathological state (Medina, 2018). From the neuroscience research field, we could say that our survival depends on the information and memories saved in our brain based on previous experiences.

Despite several psychostimulants, such as cocaine, amphetamines or methylphenidate, increase extracellular dopamine (DA) levels within the brain reward circuits resulting in similar physiological effects (Avelar et al., 2013; Kahlig and Galli, 2003; Volkow et al., 2019; Wise, 2008), they do so by acting via different mechanisms. Much attention has been focused on understanding how appetitive memories consolidate and how long they remain in time, particularly given their importance in the development of addictive behaviors as well as in the relapse of such behaviors. Dopaminergic neurons of the Ventral Tegmental Area (VTA) are crucial components of the brain network involved in reward-related behaviors and participate in the generation of new memories (Jiang et al., 2018; Rossato et al., 2009; Salamone & Correa, 2012; Schultz et al., 2002). On the other hand, it has been shown that DA exerts a key control on the durability of memories by activating its receptors in brain structures critical for erasing consolidated memories, such as the hippocampus (HP) (Castillo Díaz et al., 2019; Kramar et al., 2014). In this review, we will provide evidence about the bidirectional role of DA in the generation of new memories as well as in the deletion of consolidated memories.

2. Topography of the dopaminergic system and its neuronal diversity in the brain

DA receptors are GPCRs (receptors coupled to G-protein) that can be classified in two major classes: D1-like and D2-like families. D1-like family comprises D1 and D5 subtypes (Sunahara et al., 1991) while D2 family is composed of D2, D3 and D4 receptors (Missale et al., 1998). The D1 excitatory receptors (D1R) are coupled with Gs and Gq proteins (Seeman, 1980; Seeman & Van Tol, 1994) while the D2 inhibitory receptors are coupled with Gi protein (Sibley et al., 1993; Vallone et al., 2000).

The mammalian dopaminergic system is characterized by three different circuits that can be classified as follows: the *dopaminergic-motor system,* which involves the projections from the substantia nigra to the striatum (mainly affected in Parkinson's disease) that mediate motor coordination and learning (Gerfen, 1992; Vallone et al., 2000); the *dopaminergic-endocrine system,* which involves the arcuate nucleus, the paraventricular nucleus and the media eminence regulating prolactin secretion (Vallone et al., 2000) and, finally, the most important regarding the purpose of this article, the *dopaminergic-behavioral system,* which involves mesocortical and mesolimbic systems, both originating in the VTA but projecting to different structures involved in learning and memory (Di Chiara, 2002; Nader et al., 1997; Salamone & Correa, 2012). The mesolimbic DA system originates from cells of the VTA that innervate the septum, the amygdala, the HP, and the nucleus accumbens (NAc). Two different regions can be distinguished in the NAc, the shell and the core (Di Chiara, 2002; Li et al., 2018; Zahm & Heimer, 1993), as they respond in a different way to appetitive stimuli such as sucrose, food or drugs of abuse (Bassareo et al., 2015; Cannella et al., 2018; Di Chiara, 2002; Torregrossa and Taylor, 2013). For example, cocaine, amphetamine, morphine, heroin, tetrahydrocannabinol (THC), 3,4-Methylenedioxymethamphetamine (MDMA) and nicotine preferentially activate DA transmission in the shell subregions after exposing the animals to both contingent, i.e. active substance administration, or non-contingent, i.e. passive substance exposure (Aragona et al., 2008; Lecca et al., 2007; Pontieri et al., 1995; Tanda et al., 1997). Responses to substances of abuse are also modulated by the exposure time and administration mode, and consequently DA responses may also be changed:

for example, intermittent cocaine self-administration but not long-access self-administration sensitize DA neurotransmission (Carr et al., 2020; Kawa et al., 2019). Whether NAc shell and core DA neurons regulate independently from each other or cooperatively Pavlovian learning remains unclear: the activation of D1R in the NAc shell is involved in the regulation of Pavlovian reward-incentive learning through pre- and post-trial consolidation mechanisms (Bassareo et al., 2002; Bassareo and Di Chiara, 1997), indicating that release of DA in the shell might be implicated in the association between the rewarding properties of a stimulus and its biological outcome. At variance from NAc shell, it has been proposed that NAc core plays an essential role in instrumental responding; however, it may also regulate Pavlovian associations since dopaminergic or excitotoxic lesions in the NAc core, but not shell, disrupt Pavlovian influences on appetitive behavior (Dalley et al., 2002; Parkinson et al., 2000). Also, the activation of DA projections in the NAc core, but not in the NAc shell, was sufficient to promote a Pavlovian conditioned response (Saunders et al., 2018). Interestingly, two different neuronal DA populations projecting from the VTA to the NAc core or NAc shell have recently been described. Of note, only the inhibition of these VTA-core projecting neurons facilitates the acquisition of an instrumental response and Pavlovian reward association whereas, on the other hand, stimulation of the VTA-shell-projecting neurons is able to promote an instrumental responding once the association had been previously established (Heymann et al., 2020). In addition, NAc core processes cue-selective encoding: in fact, D1R blockade in the core, but not in the shell, attenuated cue-induced reinstatement in a non-drug environment after extinction of lever presses without this cue. On the other hand, D1R blockade in the shell attenuated context-induced reinstatement of heroin seeking, whereas D1R blockade in the core was ineffective (Bossert et al., 2007). Another difference that can be noted regarding the functional role of these subregions is that they play unique roles in guiding motivated behaviors: the core seems to be involved in learning and action during a goal-directed behavior while the shell function is related to hedonic or motivational value (Castro et al., 2015; Saddoris et al., 2015; Zorrilla and Koob, 2013).

The mesocortical DA system is formed by VTA DA neurons projecting to the medial prefrontal cortex (mPFC), cingulate and perirhinal cortex. Several studies suggest that different functions of the VTA are

144 mediated by diverse subpopulations of VTA neurons that are associated with distinct neuronal
145 networks (Morales and Margolis, 2017): optogenetic approaches in transgenic rodents have
146 demonstrated different VTA neuronal subpopulations that seem to have distinct roles in aversion,
147 reward, motivation and learning (Berrios et al., 2016; Root et al., 2014; Stamatakis et al., 2013; Wang
148 et al., 2015). Traditionally, it was thought that VTA neurons were all dopaminergic neurons based on
149 the presence in the cells of the enzyme tyrosine hydroxylase (TH), responsible of DA synthesis.
150 However, recent studies have described new populations of VTA neurons: VTA-GABA neurons (Berrios
151 et al., 2016; Stamatakis et al., 2013; Tan et al., 2012), which are capable of synthetizing GABA by the
152 enzyme glutamate decarboxylase 1 (GAD1), and VTA-glutamate neurons (Qi et al., 2016; Wang et al.,
153 2015), which express the vesicular glutamate transporter 2 (vGLUT2). Both groups of cells have been
154 implicated in reward and aversion processes: VTA-GABA neurons increase their firing rate when
155 animals are exposed to cues that predict reward (Cohen et al., 2012) but they also show a transient
156 increase in response to aversive stimuli. In fact, VTA-GABA neurons inhibit VTA-DA neurons when an
157 aversive stimulus is presented during an aversive conditioning session resulting in place aversion
158 responses (Barrot et al., 2012; Tan et al., 2012; Ungless et al., 2004). In addition, it has also been
159 proposed a role of the Lateral Hypothalamus (LH) glutamatergic inputs to the VTA-GABA neurons that
160 will reduce DA release in the NAc generating place avoidance responses (Nieh et al., 2016). Moreover,
161 VTA-glutamatergic neurons are responsible and necessary for defensive responses in the presence of
162 a threatening stimulus (Barbano et al., 2020) and optogenetic activation of these neurons projecting
163 to the NAc produces aversion by activating GABA interneurons that release GABA onto medium spiny
164 neurons (MSNs) (Morales and Margolis, 2017; Qi et al., 2016). On the contrary, selective activation of
165 VTA-glutamatergic neurons in mice induces CPP through the positive modulation of VTA-dopaminergic
166 neurons (Wang et al., 2015) and plays a key role on sleep and wakefulness regulation (Yu et al., 2019).
167 Taken together, these studies indicate that VTA-glutamate and VTA-GABA neurons interact with each
168 other and regulate multiple behavioral responses (see Table 1).
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171 *2.1 Dopamine and appetitive memories formation*

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173 DA neurons in the VTA play, indeed, an important role in several, albeit different, functions including
174 motivation, incentive and stimulus salience, rewarding and aversive behaviors, as well as memory
175 processing (Rossato et al., 2009; Salamone and Correa, 2012; Schultz et al., 2002; Wise, 2004).
176 Memory is not a single-step process, but it involves complex mechanisms that can be divided in, at
177 least, four stages: acquisition (encoding), consolidation (formation), storage and retrieval. Two
178 important consequences of memory retrieval are reconsolidation and extinction (Dudai, 2004).
179 Reconsolidation refers to the process by which consolidated memories, which are insensitive to
180 amnesic agents, could revert into a vulnerable or labile state if they are retrieved and consequently
181 undergo another consolidation process (Alberini and Ledoux, 2013; Nader et al., 2000). Memory
182 extinction, on the other side, occurs when a continuous re-exposure to the conditioned stimulus
183 without the unconditioned stimulus initially generates the conditioned response but it gradually
184 decays over time (Myers and Davis, 2002). Regarding the temporal duration of memories, they could
185 be classified in short-term memories (STM), long-term memories (LTM) or persistent LTM. Mainly,
186 STM does not require the activation of the neural plastic mechanisms like protein synthesis, being
187 insensitive to mechanisms that may somehow alter gene transcription or translation. This type of
188 memories lasts between 2 and 3 hours after the acquisition. LTM, on the other hand, are not
189 immediately established after the acquisition; in fact, they require a consolidation phase, i.e.
190 molecular events that depend on protein synthesis (Izquierdo et al., 2002). These memories could last
191 from a few days to a few weeks. Lastly, persistent LTM are a particular type of LTM that could last
192 weeks, months or even the whole life (McGaugh, 2000).
193 The dopaminergic system has a central role in the acquisition and consolidation of appetitive
194 behaviors, and it is strongly affected by drugs of abuse. Unconditioned rewarding stimuli such as
195 cocaine, nicotine, morphine and amphetamines have different pharmacological effects, however they
196 all generate an increase in the DA concentration in the synaptic cleft of NAc neurons (Nader et al.,
197 1997; Pascoli et al., 2015; Salamone and Correa, 2012; Wise, 2004), primarily in the medial shell (Di

198 Chiara and Bassareo, 2007; Stuber et al., 2005). Several groups have demonstrated that DA release
199 from the VTA into the NAc is crucial for appetitive memory formation: classical studies have shown
200 that the rewarding effects of self-administered cocaine are attenuated or blocked by lesions or
201 infusions of DA antagonists into the NAc (Caine and Koob, 1994; Ito et al., 2004; Pettit et al., 1984).
202 VTA-DA neurons release DA in different target structures but also in the VTA itself, a process known as
203 somato-dendritic release of DA (Adell and Artigas, 2004; Rice and Patel, 2015; Wise, 2004). This
204 process allows VTA-DA neurons to integrate different excitatory and inhibitory afferent signals coming
205 from collaterals arising from substantia nigra DA neurons as well as from somata and dendrites of
206 VTA-DA neurons, regulating the own firing of DA neurons, as well as DA release in downstream
207 terminal fields. Drugs of abuse like cocaine or amphetamines increase extracellular DA at the level of
208 the dendrites in the VTA (Kalivas and Duffy, 1989). Synaptic DA will target mainly D1Rs located on
209 GABA and glutamate axon terminals originating in other regions of the brain and impinging on VTA DA
210 and non-DA neurons (Harrison et al., 1990; Lu et al., 1997). Consequently, somatodendritic DA release
211 via D1R modifies GABA and glutamate release in the VTA, which, as a result, regulates DA neuronal
212 firing (Kalivas and Duffy, 1995).
213 Considering the meso-corticolimbic system, mPFC and striatal neurons are involved in reward-based
214 associative learning (Histed et al., 2009; Puig et al., 2014). The blockade of both D1R and D2R in the
215 monkey's PFC results in learning deficits that correlates with alterations in the normal neuronal
216 oscillatory activity of these cells (Puig et al., 2014). It has recently been shown that D1R antagonism
217 also impaired learning on a spatial food-rewarded task and that the activation of these receptors by a
218 D1R agonist infusion results in a better performance of the same task (Feyissa et al., 2019).
219 Stimulation of NAc shell DA transmission by addictive drugs is also shared by natural rewards like food,
220 implicating DA shell responses to feeding behaviors and tastes-responses. Hippocampal DA regulates
221 appetitive memory formation too: in fact, the D1R blockade in this structure, prior to a cocaine-
222 conditioning session in a CPP task, impairs short and long-term memory formation (Kramar et al.,
223 2014). Taken together, it appears evident that dopaminergic transmission modulates appetitive
224 memories not only in purely dopaminergic areas, such as VTA, but also in other areas with lower

dopaminergic density, further emphasizing the modulatory role of this neurotransmitter on this type of memories.

2.2 Dopamine and aversive memories formation

Evidence exists that DA is not only involved in the mechanisms regulating reward but also in the regulation of aversive memories. Dopaminergic signaling positively regulates the consolidation and persistence of electrical shock-associated memories in rats: in fact, inhibitory avoidance learning triggers molecular signaling in the HP that is crucial for this type of memory formation. DA, together with β-noradrenergic and serotoninergic signaling (Bevilaqua et al., 1997; Izquierdo et al., 2006), regulates late events associated with aversive memory formation: activation of D1R 3 and 6 h after training promotes long-aversive memory, an effect blocked by the infusion of a D1R antagonist (Izquierdo & Medina 1997).

VTA-DA neurons projecting to the mPFC are not only involved in the regulation of appetitive memories, but they also modulate aversive stimuli (Burgos-Robles et al., 2013; Euston et al., 2012). DA in the mPFC plays also an important role in the regulation of shock-associated learning: activation of D1R in the mPFC during the acquisition phase potentiates such memory, an effect that make it last longer than expected (Gonzalez et al., 2014). In addition, activation of the mPFC neurons projecting to the dorsal periaqueductal gray (dPAG) is sufficient to generate place avoidance and defensive behaviors (Vander Weele et al., 2018).

It is well known that also the basolateral amygdala (BLA) regulates aversive-learning processes (Davis, 1992; Karalis et al., 2016; Lüthi & Lüscher, 2014; Maren & Quirk, 2004; Sengupta et al., 2018; Taub et al., 2018). Taking into account mPFC-BLA connections, it is important to remark that these neurons express both D1R and D2R (Land et al., 2014; Rosenkranz and Grace, 2001). In this sense, it may be possible that the BLA regulates both positive and negative valence stimuli and that different dopaminergic neural subpopulations play a role in the valence-encoding signaling in the BLA. However, further studies will be necessary to understand how stimuli are processed in this specific

circuitry. On the other hand, VTA-BLA neurons regulate the expression of conditioned fear memory through D2R-mediated mechanisms and the blockade of these receptors attenuates fear by impairing the retrieval of a learned association between light-conditioned stimulus (CS) and footshock-unconditioned stimulus (US) (de Oliveira et al., 2011; Nader and LeDoux, 1999).

In *Drosophila melanogaster,* DA signaling to the mushroom body intrinsic neurons (Kenyon cells) is critical to stabilize olfactory memory, and many groups have shown the role of this signaling on aversive-olfactory memory (Bilz et al., 2020; Perisse et al., 2013; Widmann et al., 2016). During olfactory association with a cue, even if both sugar reward and electric shock punishment are regulated by these Kenyon cells, DA is crucial for the aversive memory while DA and also octopamine (known as the homologous arthropod norepinephrine) regulates sugar appetitive memory, which mimics how aversive and appetitive learning is regulated in mammals (Liu et al., 2012; Schwaerzel et al., 2003). Homologous D1 receptor dDA1 in the mushroom body of the fly regulates both appetitive and aversive learning in the pavlovian olfactory conditioning. Abnormal dDA1 expression impairs sugar and electric shock conditionings while reinstatement of this receptor in the same subset of mushroom body neurons rescued both aversive and appetitive learning (Kim et al., 2007). Dopaminergic neurons diversity also exists in flies: three different clusters of DA neurons have been described in the fly, all connecting to the mushroom body that ends on different subdomains, that are able to induce aversive odor memory formation (Aso et al., 2012). In addition, *the expression of this dDA1 receptor on a particular type of Kenyon Cell that in the end modulates dopaminergic signaling,* is sufficient to activate short and long term memory mechanisms within the same aversive task (Qin et al., 2012).

Together, these findings show that DA also participates in the modulation of aversive memories further strengthening its multifaceted role in memory-related processes and highlighting the notion that opposite stimuli, such as appetitive and aversive, are able to trigger similar mechanisms modulated by the same neurotransmitter.

2.3 Dopamine and its interaction with other neurotransmitters: Glutamate, Acetylcholine and Serotonin

With respect to the neural processes associated to memory formation, glutamatergic transmission has been implicated in many learning processes such as spatial learning, aversive taste memory and conditioning place preference (Balschun & Wetzel, 1998; Bermudez-Rattoni, 2014; Zhang et al., 2018). In the insular cortex, glutamate plays a critical role in the regulation of appetitive and aversive taste memory (Bermúdez-Rattoni, 2004; Gal-Ben-Ari. and Rosenblum, 2012; Núñez-Jaramillo et al., 2010). In particular, regarding appetitive memory, the NMDA receptor antagonist MK-801 in the NAc was able to inhibit the reconsolidation of instrumental memory for sucrose (Piva et al., 2018). Moreover, ketamine, another NMDA receptor antagonist, given 24h prior to renewal of sucrose-seeking, significantly inhibited conditioned instrumental responding without altering the contextual memory reconsolidation. Such behavioral effect of ketamine was induced via expression changes of glutamate receptors relevant for drug-seeking and appetitive memory reconsolidation in amygdala, HP and NAc (Piva et al., 2020).

mPFC glutamatergic pyramidal neurons exhibit synaptic plasticity after repeated cocaine exposure (Huang et al., 2007; Otis and Mueller, 2017; Pena-Bravo et al., 2017), suggesting a contribution of these cells to cocaine-associated memory formation. The lack of the glutamatergic receptor mGluR5 gene leads to an expected increase of DA levels in the NAc impairing cocaine-self administration responses (Chiamulera et al., 2001). In fact, many glutamatergic projections arrive into the NAc from different structures such as the mPFC, HP or amygdala (Jong et al., 2020; Stuber et al., 2013), and electrophysiological studies have demonstrated that these glutamatergic innervations from various structures modulate the activity of the NAc GABAergic output neurons (Mingote et al., 2019; Qi et al., 2016) that will, finally, impact on the cortical activity. As we have mentioned before, VTA-DA neurons also directly modulate the activity of these NAc neurons resulting in the regulation of basic behavioral reactions underlying reinforcement. Interestingly, in the last few years, much attention has been paid to a special type of neurons able to co-release both DA and glutamate from the same cell referred also

as multiplexed neurotransmission (Mestikawy et al., 2011; Morales & Margolis, 2017; Trudeau et al., 2014). Several studies using experimental animals are focused on understanding the impact of these DA-glutamate co-release mechanisms in addiction, suggesting a new target to treat substance abuse and other psychiatric disorders (Mingote et al., 2019; Trudeau & Mestikawy, 2018).

Although it is well established that excitatory and inhibitory neurotransmitters, like glutamate and GABA, play a critical role in modulating the activity of the midbrain dopaminergic neurons, acetylcholine may modulate in the same way the dopaminergic neurotransmission. Cholinergic projections from the basal forebrain innervate cortical and subcortical structures, including the PFC (Bloem et al., 2014) that regulates attentional and cognitive processes (Bloem et al., 2014; Parikh and Sarter, 2008). Acetylcholine activity is mediated by multiple subtypes of muscarinic and nicotinic receptors that, when stimulated, are able to produce reinforcement of behavior triggered by rewarding or aversive stimuli (Hangya et al., 2015; Liu et al., 2015) and its signaling is intimately related with the reward circuitry in the brain. Nicotine activates these receptors thus sustaining tobacco addiction (Brunzell et al., 2015; Wonnacott et al., 2005) that commonly coexists with abuse of other substances. In fact, for example, inhibition of α7 acetylcoline receptor (AChR) activity by an antagonist, infused in the ventral HP, impairs morphine-conditioned memory (Wright et al., 2018).

Lesion and classical pharmacological studies showed a role of serotonin in several cognitive and behavioral functions that include mood, aggression, appetite, rewarding memory (Lucki, 1998; Zahniser and Sorkin, 2009) and drug of abuse disorder (Higgins and Fletcher, 2003; Kirby et al., 2011; Müller et al., 2007). For many decades, several groups have investigated the role of serotonin in reward processing. DA and serotonin are both implicated in the regulation of neuronal activity and plasticity in various brain regions including the basal ganglia. Importantly, these two neurotransmitters may interact in many behavioral responses to regulate motivation. In serotonin transporter (SERT) knockout rats, elevated extracellular serotonin levels may contribute to increase the voluntary daily intake of cocaine under self-administration conditions (Verheij et al., 2018) and in a progressive ratio schedule of reinforcement (Caffino et al., 2019), thus promoting compulsive cocaine self-administration and an increase in the motivation to work for cocaine. Further, deletion of SERT

dysregulates the glutamate homeostasis in the habenula, infralimbic and prelimbic subregions of mPFC and NAc core after cocaine self-administration (Caffino et al., 2019; Caffino et al., 2021a; Caffino et al., 2021b), pointing to serotonin-glutamate interaction as a neurobiological substrate of heightened vulnerability to drug dependence. Serotonin-glutamate interaction is also critical for inducing the extinction of cocaine seeking behavior: in fact, SERT knockout rats require a higher dose of D-cycloserine, a partial NMDA receptor agonist, to extinguish cocaine-induced CPP compared to their wildtype littermates (Karel et al., 2018). Moreover, pharmacological and electrophysiological studies have shown that serotonin can inhibit or activate VTA dopaminergic neurons (Alex and Pehek, 2008; Di Giovanni et al., 2008; Tellez et al., 2012). VTA-photoactivation of serotoninergic neurons activates VTA-DA neurons increasing DA release in the NAc and as expected, it induces CPP. It is important to remark that not only serotonin is released from these terminals but also glutamate since both serotoninergic and glutamatergic receptors are necessary for the behavioral response (Wang et al., 2019). The group of Laviolette has demonstrated that an infusion of a serotoninergic agonist in the NAc, such as cannabidiol, blocks aversive memory formation and impairs the activity of VTA-DA neurons that rely on the NAc shell and GABAergic transmission in the VTA (Norris et al., 2016). Finally, it is also remarkable that since SERT is one of the most important targets for the treatment of neurological cognitive pathologies and depression-like disorders (Barnes and Sharp, 1999; Meneses, 1999), both SERT and DAT are being studied by several groups in order to find therapeutic treatments. Since the serotoninergic receptor interacts with the DA systems (Di Giovanni et al., 2010; Fink and Göthert, 2007; Pehek et al., 2006), variations of DA D2R and SERT genes modulate prefrontal efficiency during working memory and responses to antipsychotics (Blasi et al., 2015). Also, METH-induced amnesia down-regulates SERT and DAT in the HP indicating an important role of the balance in the expression of these transporters on memory formation (Tellez et al., 2012).

Although further specific interactions among these different neurotransmitters and their role on memory processes have yet to be identified, nevertheless these studies may help understanding the cellular mechanisms underlying the role played by DA in such interactions.

3. Dopamine and active forgetting mechanisms

3.1 Dopamine and appetitive memories forgetting

Learning processes result in molecular and cellular changes that will generate (or leave) a signature. Whereas the whole molecular and cellular changes that are involved in the acquisition phase of the memory are still unknown, we are aware that those changes depend on the strength and nature of that memory itself. In the recent years, many mechanisms have been described as responsible for the persistence of memories: for instance, antagonism of D1/D5 DA receptors in the HP before acquisition of the spatial task Morris-water maze inhibited memory for 6 h without altering retrieval 20 min after training (O'Carroll et al., 2006). Another mechanism involves the neurotrophin BDNF whose administration enhances long-term persistence of associative learning tasks (Bekinschtein et al., 2014, 2008) whereas delayed c-fos expression in the dorsal HP appears to regulate the persistence of an aversive spatial task like inhibitory avoidance (Katche et al., 2010). Furthermore, Gonzalez et al., 2014 have shown that modulation of the dopaminergic signaling in the mPFC does not affect memory formation but it regulates aversive memories durability from the moment of the acquisition for 6 h or 12 h in a conditioned taste aversion and inhibitory avoidance task, respectively.

A main question that is still unanswered is how many memories and engrams can be saved by our brain during lifetime: it seems reasonable that the system can regulate the memories that are stored, thereby deleting useless information. The mechanisms by which the brain is capable of erasing information are part of the so-called active forgetting mechanisms (Davis & Zhong, 2017). Traditionally, forgetting was thought to be a passive, time-dependent mechanism by which memories were deleted due to passive physiological decay generated as a result of the inability to access to the desirable trace (Anderson & Hanslmayr, 2014; Ricker et al., 2015; Wixted, 2004). Nowadays, active forgetting mechanisms have been described (for details see Davis & Zhong, 2017) as the mechanisms or sequence of events required and sufficient to erase the substrate of a memory (Medina, 2018).

During the last years, many groups have focused their attention on DA-dependent forgetting mechanisms. The first results were obtained in experiments made on *Drosophila m.* for non-consolidated memories (Berry et al., 2012). *Drosophila m.* has a dopaminergic receptor called DAMB, which is coupled to Gs and Gq signaling pathways, required for intrinsic forgetting in the fly (Himmelreich et al., 2017). It has been shown that the Rac1 signaling pathway, including Pak and Cofilin and known for its role in regulating actin dynamics, works downstream of DAMB to drive the erasure of the memory trace (Cervantes-Sandoval et al., 2020, 2016; Davis and Zhong, 2017; Shuai et al., 2010). Interestingly, Rac1 has been also implicated in active forgetting mechanisms in mice: in fact, inhibition of the Rac1 pathway in the mouse HP extended object recognition LTM for more than 72 hours while its activation provoked the decay of such memory within 24 hours (Liu et al., 2016). Rac1 activity also regulates memory in other brain regions, including cocaine-induced memories in the NAc (Dietz et al., 2013) and motor memory in the mPFC (Hayashi-Takagi et al., 2016). This implicates that Rac1 can regulate active forgetting processes for more than one type of memory.

For many years, addiction therapies focused on mechanisms that could be targeted to erase drug-related aberrant memories that trigger cocaine-seeking behaviors during abstinence. Manipulating extinction and retrieval memory processes has been proved to reduce the strength of cue-drug association (Torregrossa and Taylor, 2013). Whether the brain has an intrinsic mechanism capable of controlling cocaine-associated memories is of great importance in addiction treatment. In fact, in the last years, new evidence has pointed out that the activation of the dopaminergic system leads to the erasure of consolidated cocaine-memories: in fact, activation of D1R in the HP 12 h after a strong cocaine-training in a long-term memory generating CPP protocol deletes a memory that is expected to last, at least, for 21 days (Kramar et al., 2014). Similar results were obtained when VTA D1R were also activated immediately after learning in a cocaine-associated task, indicating that VTA DA regulates an active forgetting process from the acquisition phase (Castillo Díaz et al., 2019). On the contrary, D1R blockade in the HP and VTA was able to induce a long-lasting cocaine-associated memory, indicating that intrinsic dopaminergic mechanism will lead to the erasure of that memory (Castillo Díaz et al.,

411 2019; Kramar et al., 2014). Taken together, these results indicate that VTA-HP connections are crucial
412 for the regulation of long-term storage of appetitive-memories.
413
414 *3.2 Dopamine and aversive memories forgetting*
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416 While DA is capable of bidirectionally controlling both formation and forgetting of appetitive
417 memories, it can also modulate aversive memories in the same way. HP has been studied in depth to
418 understand its role in spatial memory regulation. New evidence has been published about its role in
419 the regulation of different contextual memories like conditioned place aversion, inhibitory avoidance
420 or fear conditioning (Chaaya et al., 2018; Chang and Liang, 2017; Guo et al., 2019; Pereyra et al., 2018;
421 Rossato et al., 2009; Valero et al., 2018). More importantly, it has been described that, in this
422 structure, neurogenesis may occur throughout the maturation of the brain into adulthood, although
423 this issue is still a subject of great controversial between different research groups. Paul Frankland and
424 his group, using both environmental and genetic interventions to increase hippocampal neurogenesis,
425 have recently shown its role in the forgetting of contextual fear memory in mice (Gao et al., 2018). In
426 addition, it has also been shown that inhibition of Rac1 GTPase activity in rat HP enhances a contextual
427 fear memory that is not normally present when animals are tested (Jiang et al., 2016). This means that
428 a normal hippocampal neural activity is responsible for the intrinsic forgetting of those aversive
429 memories, in agreement with what happens for appetitive memories. It is interesting that this brain
430 structure can also regulate aversive memories persistence in a positive way. Activation of the
431 dopaminergic signaling using a D1/D5R agonist in the HP 12 h after a weak inhibitory avoidance
432 training makes the memory to last up to 14 days. Moreover, the blockade of such DA receptors
433 impairs a long-term consolidated memory at the same time point (Rossato et al., 2009).
434 Other structures, such as lateral habenula (LHb), are also implicated in the regulation of aversive
435 memories persistence. Inactivation of this structure by infusing the GABAergic agonist muscimol
436 during acquisition impairs long-term memory without altering its formation. In addition, such a
437 memory block can be rescued by a second infusion of a dopaminergic agonist immediately after the

training in the mPFC or 12 h later in the HP (Tomaiuolo et al., 2014). Taken together, these results demonstrate a role of the LHb on aversive associative learning that may involve dopaminergic signaling modulation by several structures.

In *Drosophila m.* it has been shown that a mushroom body output neuron generates calcium depression when an odor is paired with an electric shock, and as a result animals show avoidance to that odor. Contrary, activation of the related DA neuron by an electric shock restores the normal mushroom body neuron activity causing behavioral forgetting. Thus, as it happens in mammals for appetitive memories, DA is able to bidirectionally regulate aversive learning and forgetting in drosophila (Berry et al., 2018, 2012). Zhang et al., 2008 have demonstrated an impairment of aversive olfactory memory retention in *Drosophila m.* by knocking down the DAT, presumably because of the increased DA levels in the synaptic cleft. This possibility is confirmed by the evidence that infusions of L-dopa exhibit the same effect. Yi Zhong and associates have demonstrated also in the olfactory aversive memory that a subset of dopaminergic neurons within the mushroom body neurons decreases long-term memory retention together with glutamatergic neurons activated after, but not before, training. In addition, blockade of these two neuronal subsets diminishes memory decay over a 3 h period without affecting memory acquisition (Shuai et al., 2015). Interestingly, it has been also shown that forgetting of LTM could occur in a transient manner. Artificial activation of a single DA neuron is sufficient to suppress LTM retrieval, but it recovers over time until it is accessible again. In addition, the mechanisms underlying this transient forgetting depend on the presence of interfering stimuli before the retrieval (Sabandal et al., 2021).

Altogether this evidence supports the role of the dopaminergic signaling in the modulation of long-term memory processes related with aversive-valence stimuli. In this sense, as it happens with appetitive memories, our brain is capable to control what is worth storing and what, instead, may lead maladaptive responses and consequently may be worth forgetting.

4. Dopamine signaling and molecular mechanisms of forgetting

We must bear in mind that there is no memory without forgetting and the ability to forget is, at least, as important as the ability to learn. This is crucial for many events of our life, mainly aversive events, in which it is essential to forget minute details of a given unpleasant or traumatic situation. It has also to be considered that, without memory, humans would be little but, sometimes, such memories become overwhelming and therefore the ability to forget is indeed essential and allows us to move forward. Thus, forgetting may be now considered as a memory-related process to be distinguished from encoding, consolidation and retrieval (Gravitz, 2019). Several mechanisms have been described to explain active forgetting processes. As we have mentioned, drugs of abuse produce their effects by altering the dopaminergic signaling, mimicking endogenous DA and activating the same cellular mechanisms. Moreover, it is important to remark that neurotransmitters can interact with each other; for example there is evidence that DA interacts with cortical glutamate to generate different behavioral responses: in fact, interactions between DA and glutamate were described at both presynaptic and postsynaptic sites within the striatum (Hyman and Malenka, 2001; Reynolds and Wickens, 2002). Consequently, both glutamatergic and dopaminergic responses are associated with the activation of ERK I and II, two important kinases for long-term synaptic plasticity (Thomas and Huganir, 2004; Valjent and Maldonado, 2000). Evidence exists that these kinases are involved in the regulation of the memory persistence phase on hippocampal dependent tasks (Bekinschtein et al., 2008) and, moreover, they may do it in a circadian-dependent way (Eckel-mahan et al., 2008).

DA modulates cAMP signaling that is involved in synaptic plasticity and associative memory formation (Kandel, 2001; Louis et al., 2018; Roman and Davis, 2001). In the *Drosophila m.* activation of cAMP dopaminergic pathway regulates aversive reinforcement (Sabandal et al., 2020; Schwaerzel et al., 2003). Shuai et al., 2010 have demonstrated that inhibition of Rac1 allows memory to persist longer (up to 1 day) by blocking interference-induced forgetting, as occurs with dopaminergic blockade signaling in rodents. On the other side, activation of Rac1 pathway causes memory to decay quickly,

accelerating forgetting mechanisms (Shuai et al., 2010). It is important to remark that, again, this alteration on memory erasure does not alter memory formation, excluding all the possible explanations regarding consolidation modulation of the memory. Rac1 activates an intermediate kinase (LIMK-1) that will phosphorylate cofilin at Ser3 that, in turn, will regulate actin cytoskeletal reorganization (Yang et al., 1998). Cofilin belongs to a family of F-actin depolymerizing factors that are known to break actin filaments (Bamburg et al., 1999) and, importantly, this actin-depolymerizing activity has been implicated in synaptic plasticity, spine-morphology changes and memory plasticity (Borovac et al., 2018; Lian et al., 2020; Sungur et al., 2018; Wang et al., 2019). In this sense, Rac1 active forgetting mechanisms may imply changes on cofilin phosphorylation state, which could trigger memory erasure by physiological or morphological cellular changes.

A single session training in olfactory aversive conditioning in *Drosophila m.* generates two types of memory: anesthesia sensitive memory (ASM) that lasts about 5h and anesthesia resistant memory (ARM) that lasts approximately 24h (Margulies et al., 2005). With respect to forgetting of aversive associative memories, three pairs of dopaminergic neurons from the PPL1 cluster (V1, MV1 and MP1) that project to the mushroom body inhibit this specific type of olfactory consolidated ARM memory (Isabel et al., 2004). It was proposed that these neurons could trigger cAMP production and, through PKA activity, might result in this inhibition (Plaçais et al., 2012). Interestingly, the mechanisms involved promote LTM formation. The counterbalance between these two types of consolidated memories involves oscillations between both types of neurons and exhibit synchronized ongoing activity in the mushroom body before and after acquisition, playing a dual role in learning and forgetting (Berry et al., 2012). But how ARM decay within 24 h after training is controlled? Zhang et al., (2016) have demonstrated that multi-session training produces ARM that last, at least, up to 4 days due to the inhibition of Cdc42, another protein of the Rho family. Cdc42 specifically regulates ARM forgetting without altering ARM or ASM formation nor ASM forgetting. In this sense, it seems that there are molecular mechanisms that specifically affect forgetting, while memory formation is mediated by different cell signaling pathways.

5. Conclusions

As we have discussed, DA regulates both appetitive and aversive memory formation. Classically, the dopaminergic system was known as the reward-processing center of the brain; nowadays, we know that also aversive processing relies on this neurotransmitter and its signaling, underlying a remarkable ability and a multifaceted role of DA to govern such opposite mechanisms triggered by stimuli of opposite valence. On the other hand, we have also given evidence supporting the new concept of active forgetting mechanisms for associative learning. In a physiological condition, rewarding and aversive stimuli are both counterbalanced by specific cellular mechanisms that prevent unwanted behaviors. However, under pathological conditions, a challenging situation, which involves appetitive or aversive stimuli, may lead to persistent alterations in the brain homeostasis that could trigger abnormal behavioral responses. In this sense, forgetting mechanisms could be potentially used to modulate aberrant memories and treat these maladaptive behaviors.

Thus, memory malfunctions might be also viewed as a dysregulation of forgetting processes that may lead to the erasure of more information than necessary. The notion that DA contributes to memory-active forgetting further expands the already wide range of functions performed by this neurotransmitter, reinforcing the concept that DA is undoubtedly an essential and vital nourishment for our brain.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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Figure Caption

Figure 1. Graphical abstract of the VTA connections with the different meso-corticolimbic structures and the main functions regarding each different pathway. Rewarding memory formation and persistence pathways are indicated in green; aversive memory formation and persistence pathways are indicated in red; appetitive memory forgetting pathways are indicated in blue. VTA stands for Ventral Tegmental Area; PFC stands for Prefrontal Cortex; HP stands for Hippocampus; NAc stands for Nucleus Accumbens.

VTA subpopulation neuron type	Behavioral Outcome	Reference
VTA DA neurons projecting to NAc core	• Instrumental response and Pavlovian reward associations. • Cue-induced reinstatement. • Learning during goal-directed behavior.	Bassareo & Di Chiara, 1997 Bassareo et al., 2002 Dalley et al., 2002 Parkinson et al., 2000 Saunders et al., 2018 Carelli et al., 2004 Saddoris et al., 2013
VTA DA neurons projecting to NAc shell	• Context-induced reinstatement. • Feeding and tastes behaviors. • Hedonic and motivation values.	Bossert et al., 2007 Heymann et al., 2020 Castro et al., 2015 Saddoris et al., 2015 Zorrilla & Koob, 2013
VTA DA neurons projecting to mPFC	• Reward and aversive associative learning. • Aversion memory durability. • Anxiety-like behaviors.	Histed et al., 2009 Puig et al., 2014 Feyissa et al., 2019 Burgos-Robles et al., 2013 Euston et al., 2012 Gonzalez et al., 2014

VTA DA neurons projecting to HP	• Reward and aversive memories regulation. • Spatial tasks regulation • Anxiety-like behaviors. • Fear-like behaviors.	Castillo Díaz et al., 2019 Kramar et al., 2014 O'Carroll et al., 2006 Bekinschtein et al., 2008 Katche et al., 2010
VTA DA neurons projecting to BLA	• Fear conditioning memory. • Anxiety-like behaviors.	Taub et al., 2018 de Oliveira et al., 2011 Nader & LeDoux, 1999
VTA GABA neurons projecting to VTA DA neurons; to NAc DA neurons; to mPFC neurons.	• Cue-predicted reward. • Disrupt reward consumption • Aversive conditioning response. • Control dopamine release into the NAc.	Ungless et al., 2004 Cohen et al., 2012 Barrot et al., 2012 Tan et al., 2012 Van Zessen et al., 2012 Brown & Mc Kenna., 2015 Nieh et al., 2016
VTA Glutamatergic neurons projecting to NAc	• Defensive responses following a threating stimulus. • Aversion response by activating GABA interneurons.	Barbano et al., 2020 Morales & Margolis, 2017 Qi et al., 2016
VTA Glutamatergic neurons projecting to DA neurons	• Induction of place preference. • Control of sleep and wakefulness.	Wang et al., 2015 Yu et al., 2019

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1111 Table 1. Diversity within the VTA neuronal subtypes and their related behavioral outcome.

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