Medial prefrontal cortical control of reward- and aversion-based behavioral output: Bottom-up modulation

Verónica Pastor[1,2] | **Jorge Horacio Medina**[1,3]

[1]CONICET-Universidad de Buenos Aires, Instituto de Biología Celular y Neurociencia "Prof. Eduardo De Robertis" (IBCN), Buenos Aires, Argentina

[2]Universidad de Buenos Aires, Facultad de Medicina, Departamento de Ciencias Fisiológicas, Buenos Aires, Argentina

[3]Instituto Tecnológico de Buenos Aires (ITBA), Buenos Aires, Argentina

Correspondence
Verónica Pastor, IBCN (UBA-CONICET), Facultad de Medicina, Universidad de Buenos Aires, Paraguay 2155, 3er piso, Sector M3, (C1121ABG) Buenos Aires, Argentina.
Email: verpastor@fmed.uba.ar

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Abstract

How does the brain guide our actions? This is a complex issue, where the medial prefrontal cortex (mPFC) plays a crucial role. The mPFC is essential for cognitive flexibility and decision making. These functions are related to reward- and aversion-based learning, which ultimately drive behavior. Though, cortical projections and modulatory systems that may regulate those processes in the mPFC are less understood. How does the mPFC regulate approach-avoidance behavior in the case of conflicting aversive and appetitive stimuli? This is likely dependent on the bottom-up neuromodulation of the mPFC projection neurons. In this review, we integrate behavioral-, pharmacological-, and viral-based circuit manipulation data showing the involvement of mPFC dopaminergic, noradrenergic, cholinergic, and serotoninergic inputs in reward and aversion processing. Given that an incorrect balance of reward and aversion value could be a key problem in mental diseases such as substance use disorders, we discuss outstanding questions for future research on the role of mPFC modulation in reward and aversion.

KEYWORDS

acetylcholine, approach-avoidance conflict, dopamine, noradrenaline, serotonin, top-down control

1 | INTRODUCTION

We, as individuals, are the result of our actions, but what guides our behavior? We pursue certain emotions and avoid others. For that purpose, we assign a specific value to different environmental events, we remember that value, and we behave making a risk-benefit analysis (Bailey et al., 2016). So we pursue reward, but we are capable of decreasing the frequency or even stopping that behavior when its consequences become aversive (e.g., we pursue going out and have a nice time with family and friends, but we avoid that situation in the middle of a pandemic). This decision making under reward–aversion conflict is critical for survival. Furthermore, it highlights that rewarding stimuli are not always reinforcers and aversive stimuli are not always punishers, but it may depend on the individual and the context. Then, how do we make decisions to manage pleasure–harm balance? We need our prefrontal cortex (PFC) well-connected and well-modulated to provide top-down control of motivated behaviors.

Abbreviations: 5HT, serotonin; ACh, acetylcholine; Amy, amygdala; BF, basal forebrain; BLA, basolateral nucleus of the amygdala; CPP, conditioning place preference; DA, dopamine; DAT, dopamine transporter; dPAG, dorsal periaqueductal gray; DR, dorsal raphe nuclei; IL, infralimbic cortex; LC, locus coeruleus; LDT, laterodorsal tegmental nucleus; LHb, lateral habenula; MDT, mediodorsal nucleus of the thalamus; mPFC, medial prefrontal cortex; NA, noradrenaline; NAc, nucleus accumbens; NR, nucleus reuniens; PAG, periaqueductual gray substance; PFC, prefrontal cortex; PL, prelimbic cortex; PVT, paraventricular nucleus of the thalamus; RMTg, rostromedial tegmental area; SUD, substance use disorder; vPAG, ventral periaqueductal gray; VTA, ventral tegmental area.

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The PFC has been studied for decades, and it has classically been viewed as a key player on "executive" functions including attention (Muir et al., 1996), working memory (Floresco et al., 1997; Goldman-Rakic, 1995; Granon et al., 1994; Seamans et al., 1995), behavioral flexibility (Seamans et al., 1995), goal-directed behavior (Dalley et al., 2004), and decision making (Euston et al., 2012; Walton et al., 2002). It has also been described as a key player on long-term memory retrieval (Rugg et al., 1996; Tomita et al., 1999). However, its role on memory process is much more complex. It is already known that the medial prefrontal cortex (mPFC) is involved in memory acquisition (Pastor et al., 2021; Spellman et al., 2015; Zhang et al., 2019) and consolidation (Touzani et al., 2007; Tronel & Sara, 2003), likely through precise mPFC output populations (Otis et al., 2017; Ye et al., 2016).

The medial part of the PFC (mPFC) receives sensory information and integrates it with previously learned emotional values (Miller & Cohen, 2001). Two important questions arise when trying to understand the behavioral choices that promote survival. First, how does the mPFC switch between reward-seeking and punishment-avoiding behaviors? Despite previous studies about the role of the mPFC in reward (Tzschentke, 2000) or aversion (Milad & Quirk, 2002), we are only starting to comprehend some of the processes that will get us closer to an answer. Circuit manipulation tools (e.g., optogenetics and chemogenetics) have emerged during the last decade to manipulate long-range projections and test their contributions to stimuli-induced behavior. These studies showed that different mPFC subregions or even neuronal populations participate in promoting reward-seeking or punishment-avoidance behaviors by activating different downstream circuits (Capuzzo & Floresco, 2020; Rozeske et al., 2018; Vander Weele et al., 2018; Warden et al., 2012; Ye et al., 2016). Nevertheless, the same mPFC neurons could also be engaged in both rewarding and aversive experiences (Del Arco, 2020). Noteworthy, a smart combination of modern technologies including genetic and imaging techniques started to bring a whole-brain analysis of neural pathways activation during behavior (Kim et al., 2017; Ye et al., 2016). A second question is: how the activation of specific subcortical circuits is regulated during behavioral choices that promote survival? Neuromodulatory systems in the mPFC are likely essential players (Vander Weele et al., 2018). However, how mPFC bottom-up modulation contributes to mPFC role in reward- and aversion-based behavior is not completely understood. Importantly, an impairment of those processes may be associated with neuropsychiatric diseases including anxiety, depression, posttraumatic stress disorder, or substance use disorder, just to name a few.

Thus, the goal of this review is to advance in the comprehension beyond previous studies by consolidating and discussing behavioral, pharmacology, and circuit-based findings, to provide an overview of the role of mPFC in reward- and aversion-based behavioral control. We first outlined anatomical features of the mPFC, including projection pathways involved in reward and aversion processing. Then, we went through recent findings from pharmacology and circuit neuroscience. We discussed how different neural pathways and their modulation would make the mPFC a major integration hub of reward and aversion processing. Finally, a great body of evidence tempted us to suggest that dopaminergic inputs to the mPFC—probably in combination with other neuromodulators—constitute the modulatory pathway which biases the direction of behavioral output toward to approach or avoidance by gating the top-down control of thalamic, epithalamic, basal ganglia, and brainstem nuclei.

2 | mPFC ANATOMICAL ORGANIZATION

To understand the role of the mPFC in rewarding and aversive processing, we need to know the anatomical organization of this brain area and its projection targets. The PFC is highly conserved across mammals. The rodent mPFC is considered functionally homologous to the human dorsolateral PFC (Farovik et al., 2008; Uylings et al., 2003), which is involved in decision making (Barraclough et al., 2004). However, there is a lack of congruence in the literature regarding anatomical definitions which may difficult the comparative analysis between species (Laubach et al., 2018; van Heukelum et al., 2020). Still, studying the PFC in rodent models continues to be a crucial step for understanding human health and disease. The rodent PFC has been divided into medial and lateral parts, where the medial part—the mPFC—consists of three subregions: the ventral part of the anterior cingulate cortex, the prelimbic cortex (PL), and the infralimbic cortex (IL) (Öngür & Price, 2000; Uylings & Van Eden, 1991).

The mPFC is composed of several neuronal subtypes. Broadly, they can be classified as excitatory—glutamatergic—pyramidal neurons and inhibitory—gabaergic—interneurons (Somogyi et al., 1998). Within the mPFC microcircuitry, the neuronal balance between excitation and inhibition is crucial for proper cognitive processing (Yizhar et al., 2011). This excitatory/inhibitory balance is highly affected by classical neuromodulators, including dopamine (DA), noradrenaline (NA), acetylcholine (ACh), and serotonin (5HT). Gabaergic interneurons have been classified based on the expression of molecular markers including somatostatin, parvalbumin, calretinin, or vasoactive intestinal peptide (Kawaguchi & Kondo, 2002). These interneurons form not only a local inhibitory control of pyramidal activity but also local neuromodulation by neuropeptides. During the last decade, attention to the study of inhibitory interneurons in the mPFC has increased, focusing on disinhibitory circuits (Anastasiades

et al., 2019). However, it is currently unclear whether classical modulatory systems primarily regulate inhibitory or disinhibitory networks, which is critical to understand mPFC function. Moreover, despite the fact that gabaergic neurons in the mPFC have been mostly considered as local players, there is evidence of a subpopulation of gabaergic neurons projecting outside the PFC (Lee et al., 2014). In this review, we focused on the role of glutamatergic projection neurons, but for latest findings on prefrontal interneurons, we encourage the reader to see recent reviews on this topic (Cardin, 2019; Ferguson et al., 2018). It is important to note that pyramidal neurons in the rodent cortex have characteristic gene expression profiles (Baker et al., 2018). However, contrary to interneurons, they have not yet been functionally studied in the mPFC considering differential molecular markers (but see Kim et al., 2017; Ye et al., 2016). These studies could probably increase our knowledge about specificity and function of pyramidal neurons subtypes.

The mPFC is a multilayered structure, and differently from other neocortical areas, it lacks Layer 4 (Radnikow & Feldmeyer, 2018). This layer segregation is based not only on cytoarchitectonic features such as the size and location of the pyramidal cell bodies, but also on other features such as gene expression or functional properties (Radnikow & Feldmeyer, 2018; Uylings et al., 2003). Differential projection targets involved in reward and aversion sometimes arise from different mPFC layers (Gabbott et al., 2005; Kim et al., 2017; Otis et al., 2017). Neuromodulation is also layer-segregated (Han et al., 2017; Poorthuis et al., 2013). Thus, a better understanding of neuromodulation of target-specific projection neurons may be crucial to unravel mPFC control of adaptive behavior. The main source of mPFC neuromodulators arises from ascending subcortical inputs. The mPFC receives DA from the ventral tegmental area (VTA) and substantia nigra, NA from the locus coeruleus (LC), and ACh from the basal forebrain and 5HT from dorsal raphe nuclei. These inputs form the bottom-up mechanism of behavioral modulation and will be assessed below in this review.

The mPFC regulates its own neuromodulatory input by reciprocal connections with those modulatory systems in a topographical manner (Carr & Sesack, 2000; Vázquez-Borsetti et al., 2009). In addition, by influencing the output of neuromodulatory systems to other brain areas, the mPFC exerts a top-down control of the behavioral output. mPFC projection targets have been initially elucidated by circuit-tracing, imaging techniques and pharmacological disconnection studies. Carr and Sesack (2000) showed that mPFC targets: (1) VTA dopaminergic neurons which project back to the mPFC and (2) VTA gabaergic neurons which project to dopaminergic neurons innervating the nucleus accumbens (NAc). These connections constitute the mesocorticolimbic circuit. The mPFC also projects directly to the NAc (Berendse et al., 1992) and other limbic areas such as the amygdala, which projects back to mPFC or to hippocampal neurons (McGarry & Carter, 2017). In addition, the mPFC projects to several thalamic nuclei (Li & Kirouac, 2012; Vertes, 2004), to the lateral habenula (Kim & Lee, 2012; Mathis et al., 2017), to periaqueductal gray (Floyd et al., 2000), and to the dorsal raphe nuclei (Celada et al., 2001; Vázquez-Borsetti et al., 2009). These connections are involved in the mPFC-induced top-down control of behavior, as we will review below.

As we mentioned before, circuit-tracing experiments have been useful to address mPFC projection targets identification. However, the lack of specificity for identifying neuronal subtypes has limited its effectiveness. Instead, the emergence of new techniques has complemented previous work by assessing the functional diversity of prefrontal projections to subcortical regions, which represents a crucial issue when studying the mPFC involvement on emotional processing. In the next section, we address recent findings showing the implication of unique mPFC projection neurons and their targets on reward- and aversion-based behavioral output. For the purpose of this review, we will refer the precise subregion of the mPFC when this information is available.

3 | mPFC PROJECTION TARGETS AND THEIR ROLE IN REWARD AND AVERSION PROCESSING

For individuals and species to survive, behavior is driven by two essential forces: the pursuit of reward and the avoidance of punishment. These forces are not absolute. Instead, there is a spectrum of possible motivational forces ranging from an extremely intense, narrow attraction for a given target to an uncontrollable and unjustified aversion to other stimuli. Whereas reward engages approach strategies generating consummatory behaviors, aversion involves avoidance behaviors and negative feelings including fear. In this way, the mechanisms in the mPFC involved in the modulation of reward and aversion markedly influence decision making and the acquisition and storage of new information. It is worth noting that reward involves pleasure (liking) and motivation (wanting) for an approach-inducing stimulus, two processes which are differently regulated in the brain (Berridge & Robinson, 2016). Likewise, it is important to differentiate aversion from fear. The structures and mechanisms that regulate the acquisition and expression of conditioned fear do not necessarily explain all the processes that aversion entails. Furthermore, fear mainly involves passive (freezing) behaviors whereas aversion also involves active (avoidance) behaviors (Diehl et al., 2019).

Dissociable roles have been shown for different subregions of the mPFC in reward and aversion processing. There have been different findings across aversion studies, with

some showing, for example, that PL is implicated in fear expression whereas IL is implicated in fear suppression after extinction (Peters et al., 2009). The same was reported in reward studies, where PL promotes cocaine reward seeking, whereas stimulation of the IL suppresses relapse after extinction (Peters et al., 2009). However, these dissociable roles depend on the behavioral task and the nature of the stimuli. For example, different results arise when studying drugs of abuse versus natural rewards such as sucrose (Caballero et al., 2019; James et al., 2018). These discrepancies likely result from differentially targeted subcortical brain areas across studies and by several experimental limitations of lesion and microinjection studies. To overcome those issues and complementing pharmacological and lesion approaches, circuit manipulation tools have been used to manipulate long-range projections and test their contributions to stimuli-induced behavior. In this section, we review some of the key brain targets of the mPFC which are involved in behavior entailed to pursuit reward or avoid punishment. As will be seen below, even though various brain regions sense both rewarding and aversive experiences (Reynolds & Berridge, 2008) and various neural circuits are involved in appetite and avoidance behaviors controlled by the mPFC, some of them are preferably in charge of pursuing reward, whereas others are more involved in avoiding punishment (Figure 1).

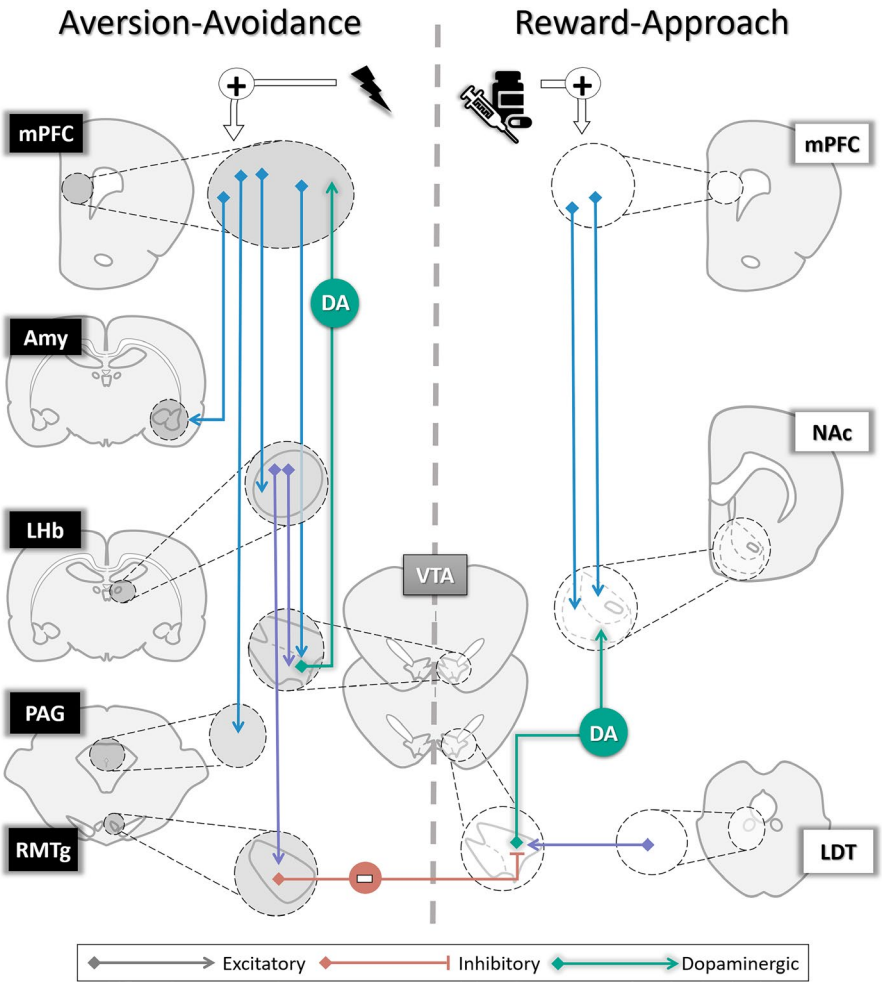

FIGURE 1 Preferential channels for aversion-induced avoidance or reward-induced approach. This figure depicts top-down pathways preferentially activated by aversive or rewarding stimuli. Left: mPFC projections to Amy, LHb, and PAG are activated by aversive stimuli (e.g., shock) and promote avoidance behaviors such as real-time place avoidance or conditioned place avoidance. Right: mPFC projections to the NAc are activated by rewarding stimuli (e.g., cocaine) and promote approach behaviors such as real-time place preference or conditioned place preference. Dopaminergic projections from the VTA to the NAc induce reward and are activated by LDT or inhibited by RMTg. Dopaminergic projections from the VTA to the mPFC which induce aversion are activated by LHb or inhibited by LDT (not shown). For simplicity, we omitted other modulatory pathways and interconnected brain areas shown in the next figures. Amy, amygdala; DA, dopamine; LDT, laterodorsal tegmental nucleus; LHb, lateral habenula; mPFC, medial prefrontal cortex; NAc, nucleus accumbens; PAG, periaqueductal gray substance; RMTg, rostromedial tegmental nucleus; VTA, ventral tegmental area

3.1 | mPFC projections to the NAc

The NAc is the ventral part of the striatum and it is densely innervated by the mPFC (Ma et al., 2020). The NAc consists of two primary components: a medial "shell" and a lateral "core" subregions, which have been proposed to mediate different behavioral functions (reviewed by Floresco, 2015). Like the dorsal striatum, the NAc is composed of different subpopulations of medium spiny gabaergic neurons expressing D1 or D2 dopamine receptors. In the NAc core, mPFC glutamatergic neurons target both D1- and D2-type medium spiny neurons but with a prominent activation of D2- over D1-expressing neurons (Deroche et al., 2020; Li et al., 2018). Additionally, anatomical studies showed that the NAc core receives input primarily from the PL, whereas the NAc shell receives input primarily from the IL (Brog et al., 1993; Voorn et al., 2004). It was shown that PL promotes while IL inhibits reward-seeking behavior after extinction (Peters et al., 2009) and that the NAc core—but not the NAc shell—mediates approach toward reward-related stimuli (Di Ciano et al., 2001; Salamone & Correa, 2012). In support of these findings, circuit manipulation studies showed that PL-NAc core projections are activated by a rewarding experience—that is, cocaine exposure—(Ye et al., 2016) and promote cocaine-seeking reinstatement in a self-administration test (McGlinchey et al., 2016; Stefanik et al., 2013). PL-NAc projections are also involved in conditioned reward-seeking expression (Otis et al., 2017). However, the panorama is even more complicated if we consider that different subpopulation of neurons from the same mPFC subregion project to different subcortical areas with diverse behavioral consequences. This was shown for IL, where different ensembles engage cocaine self-administration or its extinction, depending on the NAc subregion targeted (dorsomedial core or medial shell, respectively; Warren et al., 2019).

PL-NAc pathway is also involved in aversion-induced behavior. Martínez-Rivera et al. (2019) combined retrograde tracers with c-Fos immunohistochemistry to identify prefrontal projections activated during active avoidance. These authors found that extinction of avoidance activates both PL and IL projections to the NAc. Using the same task, Diehl et al., (2020) showed that direct projections from PL to NAc core inhibit whereas indirect PL-amygdala-NAc shell projections facilitate avoidance following tone-shock association. Interestingly, stimulating a mPFC-NAc lateral shell subpopulation of neurons which were activated by an aversive stimulus (shock) suppress reward-seeking behavior (Kim et al., 2017). Moreover, PL-NAc shell pathway is involved in suppressing reward seeking in the presence of aversion-related cues (Piantadosi et al., 2020). These findings highlight the role of the mPFC-NAc pathway in controlling behavior based on pleasure–harm balance.

The NAc integrates cognitive and emotional information from different brain areas, where glutamatergic activation by the mPFC exerts top-down control of reward-based action selection (Sesack & Grace, 2010). Notably, Lee et al., (2014) found gabaergic mPFC-NAc projection neurons which, when activated, could elicit avoidance behavior. Although these authors did not distinguish between PL and IL subregions, the canonical view of mPFC exerting top-down control of subcortical areas exclusively by glutamatergic neurons should be revised.

3.2 | mPFC projections to the amygdala

The amygdala is considered a brain hub for integration of sensory and nociceptive information (Janak & Tye, 2015; Sigurdsson et al., 2007). It can be divided into two main subnuclei, the basolateral amygdala (BLA) and the central amygdala, which play a crucial role in emotion and fear responding. During the last 15 years, a body of evidence accumulated demonstrating strong interactions between subregions of the mPFC and the amygdala in the top-down control of aversive behaviors (Do-Monte et al., 2015; Giustino & Maren, 2015). Recent findings support this concept: direct communication between the mPFC and the amygdala contributes to the acquisition and expression of trace cued fear conditioning (Kirry et al., 2020); PL neuronal manipulations modified both acquisition and extinction of morphine-induced conditioning taste aversion (Huang et al., 2020); optogenetic activation of PL-BLA pathway regulated withdrawal memory in the conditioned place aversion task (Song et al., 2019). The classical view of mPFC-amygdala circuit function on fear memory is based on a series of studies showing a dichotomy in PL and IL function: whereas PL neuronal stimulation facilitates fear expression, IL activity stimulates fear extinction and correlates with fear inhibition (Peters et al., 2009; Sierra-Mercado et al., 2011). Thus, IL region of the mPFC may play a balancing role to control morphine conditioned taste aversion and extinction. More recently, this conventional view of mPFC-amygdala function in fear has been challenged, suggesting that fear expression and extinction are not only mediated by mPFC-amygdala relationships (Do-Monte et al., 2015; Tovote et al., 2016). In short, these studies support the idea that mPFC-amygdala pathways are mainly involved in orchestrating fear memory acquisition and storage by other brain regions, such as paraventricular nucleus of the thalamus (PVT) or periaqueductal gray (PAG) (Figure 2).

Despite the amygdala classically being viewed as a brain fear-processing center (LeDoux, 1995; Sigurdsson et al., 2007), during the last decade, the role of the amygdala in rewarding processing has been highlighted (reviewed by Wassum & Izquierdo, 2015). It is likely that the

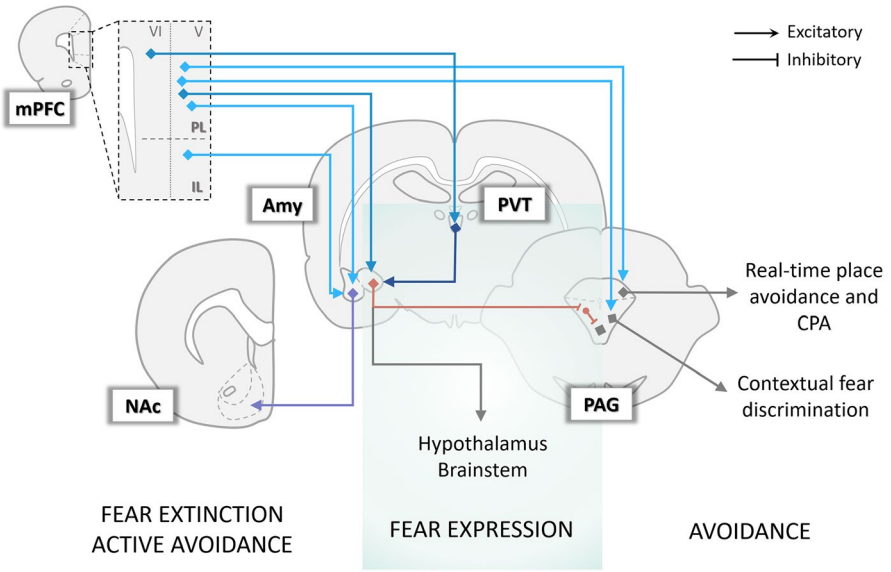

FIGURE 2 Top-down control of freezing or active avoidance in the presence of aversive context or cues. This figure summarizes mPFC-Amy interaction with other brain areas to promote aversion-based behavior: PL and IL projections to BLA are involved in fear extinction and active avoidance through the influence on NAc shell neurons; PL-CeA direct and indirect (through the PVT) projections promote fear expression through the activation of hypothalamic and brainstem areas, while inhibiting PAG neurons. Additionally, PL-PAG projections are involved in contextual fear discrimination and promote real time and conditioned place avoidance (CPA). Amy, amygdala; BLA, basolateral amygdala nucleus; CeA, central amygdala nucleus; IL, infralimbic cortex; mPFC, medial prefrontal cortex; NAc, nucleus accumbens; PAG, periaqueductal gray substance; PL, prelimbic cortex; PVT, paraventricular nucleus of the thalamus

mPFC-amygdala interconnection may function as an integrative nucleus for assessing reward–aversion conflict. Indeed, a recent pharmacology disconnection study suggested that IL projections to the BLA need to be active to prevent reward seeking when it was coupled with an electric shock punishment (Ishikawa et al., 2020). This could be related to BLA modulation of the NAc shell (Piantadosi et al., 2017), since recent evidence for PL-BLA-NAc shell circuit involvement in active avoidance (Diehl et al., 2020). Moreover, it has been recently demonstrated that motivational valence is highly plastic and involves the activation of the mesocorticolimbic circuitry controlled by the central amygdala (Warlow et al., 2020).

3.3 | mPFC projections to the lateral habenula (LHb)

Aversive experience (shock) recruits ensembles of neurons in the mPFC that control aversive behavior (Ye et al., 2016). These groups of neurons project to the PAG and to the LHb. The LHb is an epithalamic brain region activated by aversive stimuli and reward omission and inhibited by unexpected rewards (Matsumoto & Hikosaka, 2007). Both structures are involved in different features of aversion. For instance, inhibition of neural activity in the LHb blocked inhibitory avoidance memory storage (Tomaiuolo et al., 2014), whereas optogenetic activation of LHb to ventral midbrain pathway induced active and conditioned avoidance responses (Stamatakis & Stuber, 2012). These inputs impinge on VTA gabaergic neurons controlling DA neurons and inducing conditioned place aversion, an effect blocked by infusing a D1 receptor antagonist in the mPFC (Lammel et al., 2012). These results suggest that LHb signals reach mPFC via activation of DA neurons of the rostromedial VTA (Figure 1).

As occurs in almost all the central nervous system regions that participate in the modulation of aversive behaviors, there are also neurons in the LHb that sense reward stimuli or their omission (Boulos et al., 2017; Matsumoto & Hikosaka, 2007). LHb neurons are very likely to signal over reward prediction errors in the opposite way that VTA dopaminergic neurons do. That is, an increase in the activity of those neurons in LHb tends to decrease the possibility of responding with a certain behavior, whereas the decrease in neuronal activity in LHb tends to reinforce a behavior (Matsumoto & Hikosaka, 2007; Proulx et al., 2014). In addition, mPFC-LHb direct projection participates in controlling social behavior. Chemogenetic activation of the mPFC, LHb, or the prefrontal inputs to LHb suppressed socially directed behaviors (Benekareddy et al., 2018). In this context, it is interesting to mention that the LHb is connected also with the dorsal raphe nucleus (Shelton et al., 2012), a key source of serotoninergic innervation of the forebrain (see below).

3.4 | mPFC projections to the VTA

The VTA is a heterogeneous brain area with dopaminergic, gabaergic, and in a lesser extent glutamatergic neurons (Morales & Margolis, 2017). The VTA and its dopaminergic neurons projecting to the NAc have been classically been viewed as one of the pleasure centers of the brain due to their prominent role in reward processing (Schultz, 2007). Dopaminergic neurons in the VTA are involved in computation of reward prediction errors: they are activated by an unexpected reward and inhibited by a reward-associated cue when the rewarding stimulus does not arrive (Schultz, 1998; for a review, see Watabe-Uchida et al., 2017). Consistent with this, VTA dopaminergic neurons are inhibited whereas nondopaminergic neurons are excited by aversive stimuli (Ungless et al., 2004), although recent findings have identified aversion-activated dopamine neurons (reviewed by Verharen et al., 2020). The unrevealing of a huge heterogeneity on VTA subnuclei, subpopulations, and neuronal subtypes with different molecular and electrophysiological properties unveiled the complex role of the VTA on both rewarding and aversive emotional processing to promote motivated behavior. In this way, the posterior region of the VTA—the rostromedial tegmental area (RMTg), also referred to as the tail of the VTA—is enriched in gabaergic neurons involved in aversion processing. The RMTg inhibits VTA dopaminergic neurons projecting to the NAc shell and was found to encode aversive stimuli when activated by the LHb (Jhou et al., 2009; Lammel et al., 2012) (Figure 1). Interestingly, under rewarding conditions, the LHb is inhibited by VTA TH-expressing neurons which release GABA (Stamatakis et al., 2013), as we discuss in the previous section (see also Section 4.1).

These studies highlight the complex role of the VTA on reward- and aversion-based learning behavior. However, how these processes are controlled by cortical brain areas is not completely understood. The mPFC as a top-down control of VTA activity is a strong candidate. Anatomical studies showed that glutamatergic inputs from the mPFC selectively target the VTA (Carr & Sesack, 2000; Soden et al., 2020; Ye et al., 2016). Specifically, mPFC projects to (1) dopaminergic neurons that reciprocally connect with the mPFC and (2) to VTA gabaergic neurons which inhibit VTA dopaminergic neurons projecting to the NAc (Carr & Sesack, 2000). The removal of NMDA glutamatergic receptors specifically in PL-VTA projecting neurons reduces Pavlovian food conditioning in mice (Parker et al., 2011), highlighting the role of this neural pathway on reward-based learning. However, the mPFC-VTA projection has not been extensively studied in the behavioral context of reward or aversion by circuit manipulation tools. Kim et al., (2017) used a freely moving lever-press task and showed by fiber photometry that, like mPFC-NAc lateral shell pathway, mPFC-VTA projecting neurons reduced its activity upon lever-pressing with reward-receipt and increased their activity following lever pressing with shock receipt. These findings suggest that a subpopulation of mPFC-VTA projection is recruited by aversive stimuli to promote escape-related behaviors. Indeed, it was elegantly shown by Ye et al., (2016) that the mPFC have different projection neurons which are preferentially recruited after cocaine (mPFC-NAc core) or shock (mPFC-LHb) exposure, whereas mPFC-VTA projection neurons are similarly recruited by both cocaine and shock exposure. This suggests that mPFC-VTA modulates both rewarding and aversive processing. As we mentioned in the previous section, it may be possible for mPFC to regulate VTA function indirectly through the LHb. Clearly, further studies are still necessary to interrogate the precise behavioral role of mPFC projections to the VTA.

3.5 | mPFC projections to thalamic nuclei

The medial dorsal thalamic nucleus (MDT) plays a critical role in cognition through its extensive input to the mPFC. PL neurons in Layers 5 and 6 strongly drive MDT neurons that reciprocally innervate mPFC (Collins et al., 2018). MDT has long been thought as a higher order relay nucleus that transfers information about learning and decision making across the cortex (Ferguson & Gao, 2018). Among the functions that have been proposed for the MDT in connection with the mPFC are synchrony with the activity of mPFC in working memory, goal-directed behaviors, behavioral flexibility, and control of social behavior (reviewed by Parnaudeau et al., 2018).

The PL and IL subregions of the mPFC densely project to the thalamic nucleus reuniens (NR) and indirectly connect to the ventral hippocampus (Vertes, 2006). The output of mPFC to the NR has been reported to control freezing and aversive behaviors. This pathway regulates the extinction of freezing and various aversive memories (Davoodi et al., 2011; Ramanathan et al., 2018; Xu & Südhof, 2013). In addition, mPFC-NR connections control the flexibility to respond to a threat, thus facilitating adaptive coping. In order to increase the chances of avoiding threats, it is sometimes required to decrease reactive behaviors such as freezing. It has been recently demonstrated that chemogenetic inhibition of mPFC or NR activity suppresses freezing learned in another context, thereby increasing the chances of actively avoiding a threat (Ramanathan et al., 2018). Differently from prefrontal cingulate area, where direct connection with the hippocampus has been found to be involved in fear processing (Bian et al., 2019; Rajasethupathy et al., 2015), direct connection between PL-IL subregions of the mPFC and the hippocampus has not been described. Thus, NR represents an important relay station between cortical top-down signals modulating emotional contextual memory processes (Xu & Südhof, 2013).

The PVT, a midline thalamic nucleus with reciprocal connections with the mPFC and the amygdala, plays an important role in fear conditioning and extinction (Do-Monte, Quinõnes-Laracuente, et al., 2015; Figure 2). Neurons in the PVT were activated after rats were exposed to cues signaling sweetened water reward or drug reward (Hamlin et al., 2009; Igelstrom et al., 2010; reviewed by Kirouac, 2015) or exposed to aversive environment or stimuli (Yasoshima et al., 2007). Therefore, cortical inputs to the PVT originated in Layer 6 of the mPFC may relay signals related to the saliency or some other aspect of emotionally relevant events (Li & Kirouac, 2012). For example, PVT-NAc shell projections contribute to shock-induced social avoidance in a behavioral task which involves a conflict situation (Dong et al., 2020). Indeed, recent findings suggest that motivational conflict occurring when demands for approaching and avoiding a stimulus is not compatible is under the control of PVT neurons. Chemogenetic experiments revealed that inhibition of PVT neurons impeded the resolution of the conflict (Choi et al., 2019).

Optogenetic-based behavioral experiments with sucrose demonstrated that the activation of the PL-PVT pathway suppresses both the acquisition and expression of conditioned reward seeking (Otis et al., 2017). Moreover, these authors showed that PL-PVT projections are inhibited during the presentation of a reward-associated cue. Thus, an increase of mPFC-PVT activity may be involved in behavioral inhibition, whereas a decrease on mPFC-PVT activity may be necessary for allowing approach behaviors. Interestingly, some of the PL-PVT neurons had excitatory responses during the presentation of the reward-associated cue. Although it is not known the meaning of those findings, those PL neurons could be targeting different subpopulations of PVT neurons, likely differently modulated by subcortical inputs, and targeting different subcortical areas. Indeed, recent studies using a combination of circuit manipulation and calcium imaging techniques addressed the role of the PVT-NAc and PVT-amygdala pathways on reward processing. Otis et al., (2019) found that, across learning, PVT-NAc neurons develop inhibitory responses to the reward-associated cue. Interestingly, the same was found for mPFC-PVT projecting neurons and the opposite (excitatory responses) for lateral hypothalamus neurons which were shown to inhibit PVT-NAc pathway (Figure 3). These results suggest that mPFC-PVT-NAc may induce avoidance, a behavior decreased in front of reward-associated cues. However, Keyes et al., (2020) showed—by using a conditioning place preference (CPP) task—that the PVT-NAc shell pathway is necessary for morphine-associated memory

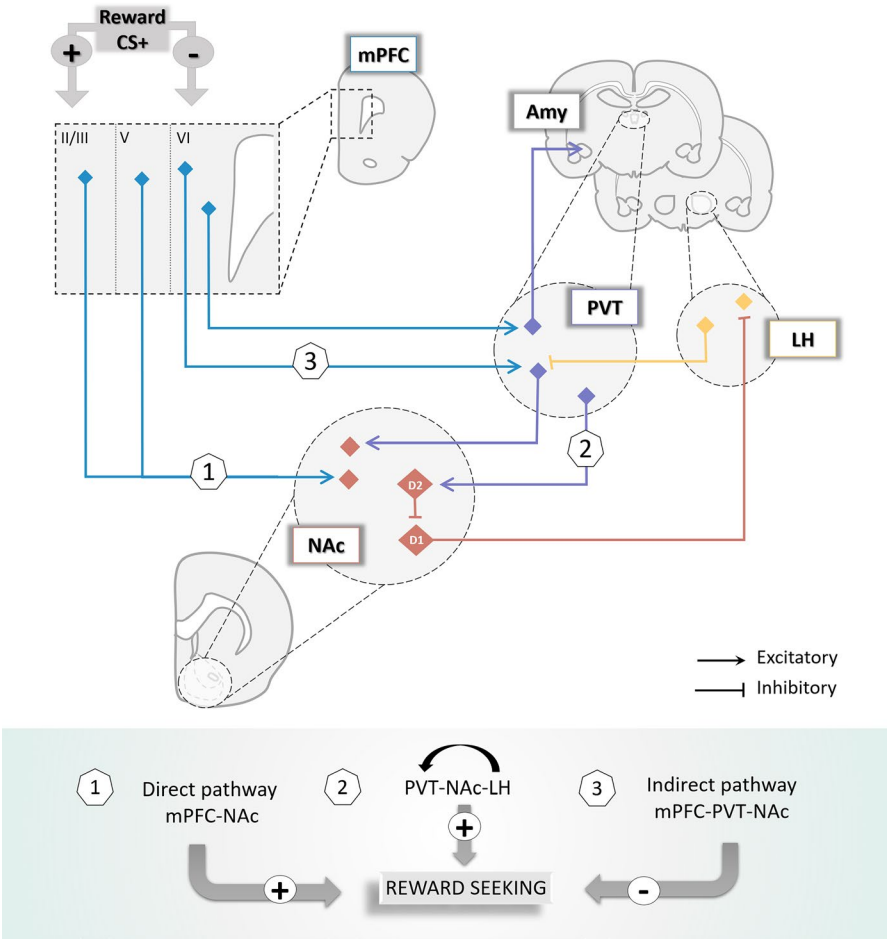

FIGURE 3 Layer-segregated mPFC neurons projecting to the NAc—directly and indirectly through the PVT—encode reward processing. (1) PL-NAc direct pathway acquires excitatory responses during the presentation of a reward-associated cue (CS+) and promotes reward-seeking behavior. (2) PVT promotes disinhibition of LH by acting on local inhibitory circuits in the NAc, a mechanism involved in reward-seeking behavior. (3) PL-PVT-NAc indirect pathway acquires inhibitory responses during the CS+ and impedes reward-seeking behavior. See the text for further description of the circuit. Amy, amygdala; D1-D2, striatal neurons expressing D1- or D2-dopamine receptors; mPFC, medial prefrontal cortex; NAc, nucleus accumbens; LH, lateral hypothalamus; PVT, paraventricular nucleus of the thalamus

retrieval and morphine-induced relapse after extinction, a process that involves disinhibition of lateral hypothalamic area (Figure 3). These authors also showed that, differently from PVT-NAc shell, PVT-amygdala pathway is necessary for morphine-CPP acquisition. However, the top-down control of these pathways was not assessed in this study. Given the high heterogeneity of the PVT, these results highlight the need for a more profound investigation on the role of PVT in reward and aversion processing, as recently reviewed by McGinty and Otis (2020).

3.6 | mPFC projections to the PAG

The PAG is involved in pain-processing, autonomic function and behavioral responses to stress or fear (Motta et al., 2017; Ossipov et al., 2010). Functionally, the PAG is composed by dorsal (dPAG) and ventral (vPAG) subregions, where the dPAG is involved in active coping or escape behaviors and the vPAG is more related to passive coping reactions like freezing (Keay & Bandler, 2015). The dPAG receives inputs from the mPFC, and this pathway is preferentially activated by aversive than rewarding stimuli (Vander Weele et al., 2018). Moreover, optogenetic activation of mPFC-dPAG pathway induces real-time place avoidance and conditioned place aversion (Siciliano et al., 2019; Vander Weele et al., 2018). This is consistent with the finding that inhibition of mPFC terminals in the dPAG drives real-time place preference (Siciliano et al., 2019). These findings suggest that, when facing an aversive stimulus or context, the activation of mPFC-dPAG pathway will drive escape-related behaviors (Figure 2). Interestingly, Rozeske et al., (2018) identified a subpopulation of PL-vPAG projecting neurons involved in switching between high and low fear states during contextual transitions in a changing environment (i.e., fear context discrimination). Briefly, these authors showed that the recruitment of the PL-vPAG pathway is necessary and sufficient for differentiate safe and unsafe environmental contexts, where an increase of PL activity occurs in a safe context (i.e., when freezing is low). Despite these results suggest that the activation of PL-vPAG pathway may reduce fear expression in that context, these authors did not observe the same results in other fear tasks (Rozeske et al., 2018). However, as was shown by Tovote et al., (2016), glutamatergic neurons of the vPAG do mediate both learned and innate freezing behavior when they are disinhibited by amygdala projections to vPAG gabaergic interneurons (Figure 2). Then, it is remarkably as we mentioned for other mPFC projection targets that the differentiation of the mPFC target subregion and cellular subtype is essential to understand its role on behavior. In this way, recent work suggested that the PAG is also involved in reward processing (Tryon & Mizumori, 2018), although the mPFC top-down control over PAG-mediated reward has not been assessed.

3.7 | mPFC projections to the cerebellum

The cerebellum comprehends the cerebellar cortex and the deep cerebellar nuclei, where the Purkinje cells project from the cerebellar cortex to the deep nuclei forming the cerebellar output to diverse brain regions (D'Angelo, 2018). Cerebellar inputs to the Purkinje cells arise directly from the inferior olive complex through the climbing fibers, and indirectly from pontine nuclei, which synapse with granular cells via mossy fibers (D'Angelo, 2018). The existence of a PFC-olivo-cerebellar pathway has been suggested by electrophysiological studies (Watson & Apps, 2019; Watson et al., 2014). Moreover, despite it is unclear if a direct cerebellar input from the PFC exists, indirect pathways have been described (Kelly & Strick, 2003; Strick et al., 2009).

The cerebellum is very well known for its role in sensory-motor integration and motor learning (D'Angelo, 2018). Several studies with imaging techniques have shown an increase on cerebellum activity in human addicts when exposed to drug-related cues (Anderson et al., 2006; Grant et al., 1996; Kilts et al., 2001; Schneider et al., 2001; Tomasi et al., 2015; Wang et al., 1999). However, those findings have been overlooked for many years. Interestingly, the cerebellum has recently received much more attention because of its emerging role in reward-related cognitive processing in preclinical studies (Gil-Miravet et al., 2019; Wagner & Luo, 2020). Increasing evidence emerged showing that the cerebellum receives reward size- and reward expectation-related information from cerebellar climbing fibers and granule cells (Larry et al., 2019; Wagner et al., 2017). It has been recently reported that a cerebellum-VTA pathway activation by optogenetics drives conditioned place preference, suggesting that cerebellum-VTA activation is rewarding (Carta et al., 2019). Thus, it may be possible that direct or indirect mPFC-cerebellum activation could be recruiting VTA dopaminergic neurons to drive reward. However, it is still unclear how cortical inputs arrive the cerebellum and how does the cerebellum integrate that information for affecting the rewarding system. Defining functional connections between the mPFC and the cerebellum would allow a more comprehending view of how these brain regions interact to drive reward-based behavior.

3.8 | mPFC projection targets in reward and aversion: Concluding remarks

In general, viral-vector studies investigate a single circuit function, for example, mPFC-PAG involvement in punishment/

aversion or mPFC-NAc in reward-approaching processing. However, an unanswered question is how the mPFC shifts from a goal-directed action pursuing reward to a top-down controlled stop of that action if it brings harm consequently, or on the other hand, how the mPFC gates the approach to stimuli or context which will not bring harm consequently anymore. The mPFC likely moves the balance within a continuum spectrum of reward- and aversion-based behavioral output. Thus, it would be important to study the same neuronal population (e.g., identified by genetic markers or by recording in vivo activity patterns) in different situations, when rewarding and aversive stimuli are present. This will allow deciphering whether or not neuronal assemblies projecting to subcortical regions pursuing reward- or aversion-based behaviors are overlapping (or superimposed). Indeed, the field is moving to a broader understanding of mPFC function, for example, in a conflict environment (for a recent review, see Bravo-Rivera & Sotres-Bayon, 2020). This also highlights the importance of studying different circuits and situations in the same setting (Li et al., 2019). This is especially important considering neuropsychiatric diseases which involve maladaptive behaviors, including approach despite negative harm (such as addictive disorders) or avoidance of safe stimuli or context (such as generalized fear and anxiety disorders). The emergence of studies using broad brain analysis tools combining genetic and imaging techniques (Renier et al., 2016; Ye et al., 2016) will probably help address this issue. Still, pharmacological approaches assessing mPFC modulation are critical for understanding how the mPFC could bias the flow of information from one pathway (i.e., promoting reward-seeking) to another (i.e., avoiding punishment). This is crucial considering that mPFC behavioral control is under the influence of bottom-up circuits which differentially modulate specific cortical outputs. In the next section, we summarize how modulatory systems influence mPFC neurocircuit and their importance on mPFC function in reward and aversion.

4 | MODULATORY SYSTEMS IN THE mPFC: HOW DO THEY SHAPE mPFC CONTROL OF BEHAVIOR?

Modulatory systems in the mPFC have a crucial role in healthy individuals, and their impairment leads to many neuropsychiatric diseases (Koukouli & Changeux, 2020; Sara & Bouret, 2012). Therefore, it is of great importance understanding how they contribute to reward and aversion processing and, finally, to guide behavior. Animal research has improved our knowledge on those mechanisms through pharmacology and metabolic studies. Previous reviews have outlined the importance of DA (Hu, 2016; Vander Weele et al., 2019), NA (Chandler et al., 2014), ACh (Del Arco & Mora, 2008; Bloem et al., 2014; Logue & Gould, 2014; Picciotto et al., 2012), and 5HT (Aznar & Hervig, 2016; Bekinschtein & Weisstaub, 2014) as neuromodulators of the mPFC. Conversely, there is still a gap of knowledge of how those neuromodulators specifically interact to modulate mPFC projection neurons and the consequent behavioral output. This is possibly because neuromodulators act through different types of receptors which are specifically expressed in different layers and cell subtypes in the mPFC (reviewed by Radnikow & Feldmeyer, 2018), which also may have different projection targets. During the last decade, viral-vector-based technology has improved our knowledge on neuronal circuits and specific projection targets, and the combination with pharmacology studies shed light on the mechanisms behind mPFC output modulation. In this section, we review recent findings on the role of modulatory systems in the mPFC and the top-down pathways which may be involved in reward- or aversion-induced behaviors.

4.1 | Dopaminergic modulation of the mPFC

Dopaminergic signaling in the mPFC is implicated in several cognitive processes, including attention, behavioral flexibility, and cue discrimination (Popescu et al., 2016; Winter et al., 2009). Therefore, a perfect balance within this system is necessary to avoid the establishment of diseases that are difficult to treat, such as hyperactivity and attention deficit disorder or substance use disorders, between others.

DA acts by its Gs-coupled D1-like (D1 and D5) or Gi-coupled D2-like (D2, D3, and D4) postsynaptic receptors, where D1 receptors were shown to activate glutamatergic mPFC neurons directly or indirectly by promoting disinhibition (Anastasiades et al., 2019; Tritsch & Sabatini, 2012). Generally, dopaminergic neurotransmission is controlled by reuptake through the dopamine transporter (DAT) and by D2 autorreceptors which are present in the presynapsis. The VTA-mPFC neurons, which constitute the mesocortical pathway, have the particularity that they lack D2 autorreceptors and have a very low expression of DAT (Lammel et al., 2008; Sesack et al., 1998). These features of VTA-mPFC neurons highlight the capacity of this pathway for maintaining a sustained high concentration of DA in the mPFC. VTA dopaminergic neurons projecting to the mPFC are reciprocally controlled by mPFC glutamatergic neurons (Carr & Sesack, 2000). As we mentioned above, VTA-mPFC pathway is also modulated by subcortical areas such as LHb, which stimulate VTA-mPFC neurons (Lammel et al., 2008), and the laterodorsal tegmental nucleus (LDT), which inhibits VTA-mPFC neurons (Omelchenico and Sesack, 2005). Although DA has traditionally been shown to be essential for reward-based learning, as we will discuss in this section, dopaminergic pathways projecting to the mPFC are involved in both reward and aversion processing.

Several pharmacologic studies with cocaine, a drug of abuse which blocks DAT, showed the importance of mPFC dopaminergic neurotransmission on reward-associated memory processing, assessed by CPP. In this regard, D1 receptors activation in the mPFC was necessary for cocaine-CPP expression (Shinohara et al., 2017) and for stress-induced enhancement of cocaine-CPP (Shinohara et al., 2018). Moreover, mPFC D1 receptors must be active for stress-induced reinstatement of cocaine self-administration after extinction (Capriles et al., 2003). Regarding mPFC targets, by combining pharmacological disconnection and c-Fos immunohistochemistry, it was shown that cue-induced reinstatement of cocaine self-administration following extinction recruited PL neurons projecting to the NAc core, a process that required DA neurotransmission in the PL (McGlinchey et al., 2016). These results are consistent with the suggested role for dopaminergic activation (via D1 receptors) of PL-NAc pathway on increasing reward sensitivity and risky choices (Jenni et al., 2017). However, these mechanisms may not be involved in natural reward seeking such as food or sucrose (Halbout et al., 2019; James et al., 2018).

On the other hand, noncanonical VTA dopaminergic pathways projecting to the mPFC, amygdala, and medial shell of the NAc (see for references Verharen et al., 2020) are activated by aversive stimuli (Lammel et al., 2012). The rostromedial part of the VTA is the main source of dopaminergic innervations to the mPFC. As mentioned previously, the activation of this pathway induces conditioned place aversion blocked by the infusion of an antagonist of D1 receptors into the mPFC (Lammel et al., 2012). To further confirm that VTA dopamine terminals in the mPFC control aversive behaviors, it was demonstrated that their direct optogenetic stimulation promoted place aversion (Gunaydin et al., 2014) and that the activation of D1 receptors in the PL immediately after subjecting rats to a conditioned place paradigm induced strong aversive behavior (Castillo Díaz et al., 2017). Additional pharmacological and biochemical experiments provide evidence for endorsing the idea that DA in the mPFC is involved in modulating aversive behaviors (Bassareo et al., 2002; Gonzalez et al., 2014). More recently, Vander Weele et al., (2018) elegantly demonstrated that DA modulates the activity of medial prefrontal neurons that project to the PAG in response to aversive stimuli, suggesting a cellular mechanism of promoting defensive behaviors. These authors proposed that mPFC dopaminergic neurotransmission locally modulates distinct neuronal populations projecting to several brain regions to select avoidance or defensive behaviors toward to respond to aversive environments or stimuli (Vander Weele et al., 2019).

It is clear from the above findings that dopaminergic modulation in the mPFC is involved in both aversion- and reward-related responses, for example, D1 activation in the mPFC is involved in contextual fear conditioning and cocaine place conditioning (Shinohara et al., ,2017, 2018; Stubbendorff et al., 2019). Thus, it will be important to deepen the investigation on the existence of different mPFC subpopulation of neurons (e.g., recruited by reward or aversion cues or stimuli) both modulated by DA, but projecting to different targets and being differently activated depending on the context. In other words, DA likely processes different types of information depending on the recruited neural circuit in which DA is acting, which also depends on the valence of the stimuli. It would be interesting to know if these DA neurons are different subpopulations or if the same neuron could respond with a different firing pattern depending on the valence of the stimuli (Figure 4). Additionally, mPFC-VTA synchrony emerges during reward-seeking behavior but is disrupted when the risk of punishment is present (Park and Moghaddam, 2017), suggesting that mPFC and VTA interact to induce inhibitory control of reward-seeking behavior under the threat of punishment. There has been a huge improvement in the knowledge of emotional circuits by assessing different cell types (e.g., dopaminergic versus. gabaergic) and different cell populations (e.g., based on projection target). Still, it is possible that the same cell type with the same projection target (e.g., VTA dopaminergic neurons projecting to mPFC pyramidal neurons) could be encoding different information (e.g., reward versus. aversion). This is probably related to the subsequent target in the circuit (e.g., VTA-mPFC-NAc versus. VTA-mPFC-amygdala) which, when recruited, promote different behavioral outputs (Figure 4). Moreover, these circuits are likely modulated by reciprocal connections with the VTA. In this regard, mPFC-VTA pathway is recruited by both rewarding and aversive stimuli (Ye et al., 2016). This may be important for conflict resolution when seeking a reward in the presence of an aversive context or stimulus.

There are still some important aspects of DA modulation in the mPFC which are not completely understood and several questions that are raised. For example, does DA act in the mPFC by modulating pyramidal neurons directly or by modifying other neuromodulators function, for example, through presynaptic terminals? Regarding pharmacological experiments, could it be possible that different D1-like (i.e., D1 and D5) receptors are modulating different mPFC cell populations? (Castillo Díaz et al., 2017). Moreover, to understand the role of dopaminergic modulation over different mPFC output targets, it is important to note that DA receptors are expressed in a layer-segregated manner and also are mPFC-specific target projections (Santana & Artigas, 2017). Another aspect that would be important to consider in future optogenetic studies analyzing dopaminergic modulation of the mPFC is that the activation of dopaminergic neurons could be inducing co-release of GABA or glutamate, making the whole picture more complicated than previously thought. Moreover, as shown in Figure 4, it is likely that other

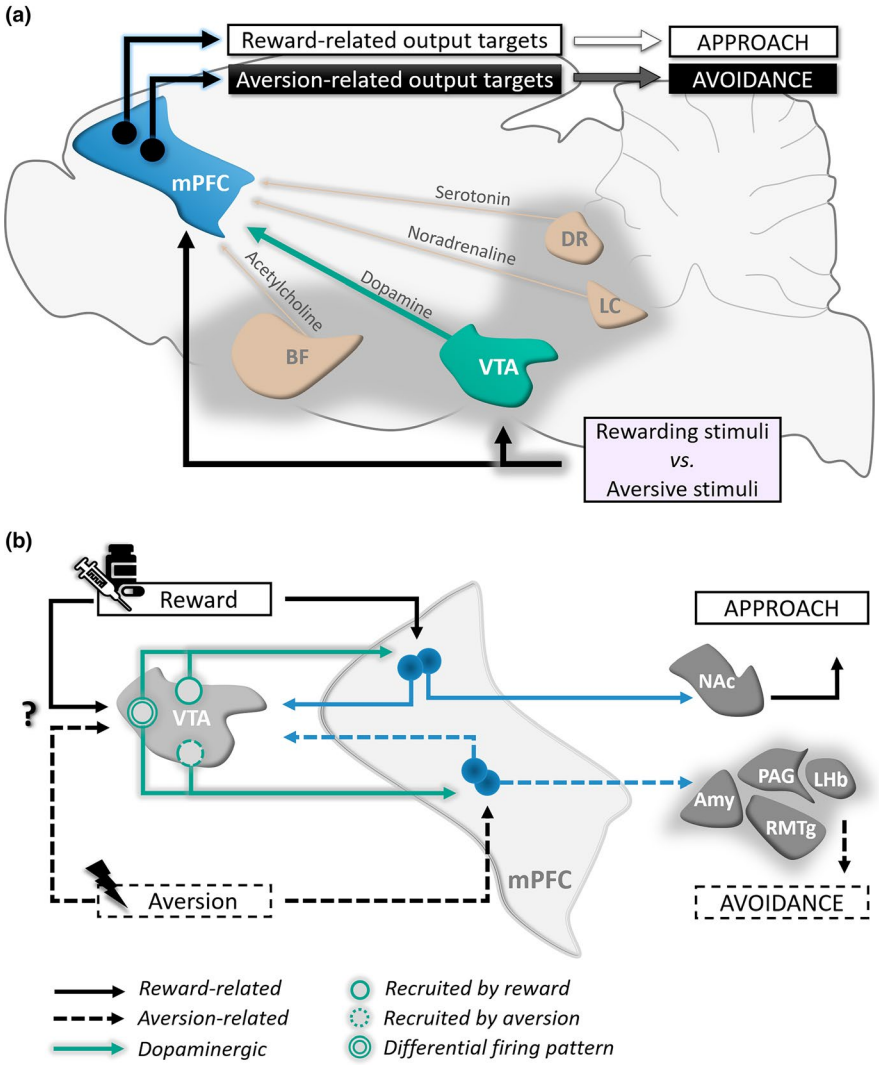

FIGURE 4 Modulation of mPFC top-down control of reward- and aversion-based behavior. (a) This figure summarizes modulatory systems which influence mPFC activity in response to rewarding or aversive stimuli and highlights that different output targets are preferably in charge of reward- or aversion-related approach/avoidance behaviors. (b) We suggest that dopaminergic system coordinates mPFC outputs to drive approach or avoidance. This may be achieved by reward- or aversion-recruited dopaminergic different subpopulation of neurons or by differential firing pattern induced by rewarding and aversive stimuli. Amy, amygdala; BF, basal forebrain; DR, dorsal raphe nuclei; LC, locus coeruleus; LHb, lateral habenula; mPFC, medial prefrontal cortex; NAc, nucleus accumbens; PAG, periaqueductal gray; RMTg, rostromedial tegmental nucleus; VTA, ventral tegmental area

modulatory systems interact with dopaminergic neurotransmission to influence mPFC control of reward- and aversion-based behavior.

In conclusion, accumulating evidence tempted us to suggest that dopaminergic inputs to the mPFC constitute the modulatory pathway which bias the top-down control of subcortical areas (thalamic, epithalamic, basal ganglia brainstem) toward approach or avoidance behavioral output (Figure 4). In conflict situations, rewarding stimuli will recruit mPFC-NAc approach pathway and aversive stimuli will recruit mPFC-Amy/LHb-RMTg/PAG avoidance pathway. It is also possible that different kinds of stimuli induce different firing patterns in DA neurons which may promote the activation of a putative loop connecting rewarding and aversive information. For example, in the presence of rewarding stimuli that induce mPFC-NAc activation, aversive stimuli may also—likely depending on the threat level—activate VTA-mPFC-Amy/LHb-RMTg/PAG pathway, biasing the behavioral direction to avoidance. If this were true, an impairment of this putative loop could be related with the development of mental diseases such as substance use disorder, where the individual takes the drug despite harmful consequences. Likely, DA acts in combination with other neuromodulators which also influence reward and aversion processing, as we discuss in the following sections.

4.2 | Noradrenergic modulation of the mPFC

Noradrenergic cortical innervation is involved in global states such as arousal and stress, which modulate memory processing (Sara & Bouret, 2012). Thus, an impairment of the noradrenergic system may bring stress-related disorders such as anxiety, posttraumatic stress disorder, and substance use disorders. Stress can be experienced by individuals exposed to an aversive stimulus (Dalley & Stanford, 1995) and can increase reward-seeking behaviors (for a review, see Mantsch et al., 2016). The LC is the sole source sending NA inputs to the mPFC (Loughlin et al., 1982), where NA increases pyramidal neurons excitability by acting on

α- (Otis et al., 2013; Wada et al., 2020) and β-subtypes (Otis et al., 2013) of noradrenergic receptors.

A growing body of evidence highlights the important role of mPFC noradrenergic system to modulate reward- and aversion-driven behavior. Pharmacology and electrophysiology studies explored the role of the noradrenergic system on reward-seeking behavior, for example, by assessing cocaine-induced CPP. Cocaine induces plastic changes in the mPFC (Ferrario et al., 2005), which are related to acquisition (Muñoz-Cuevas et al., 2013) and retrieval (Otis et al., 2018) of cocaine-associated memory. These neuroadaptations may maintain drug-associated memories to induce cue-induced seeking behavior, although the mechanisms involved are not completely understood. Noradrenergic neurotransmission in the mPFC is a strong candidate for modulating those plastic changes and affecting cocaine-memory maintenance (Fitzgerald et al., 2016; Otis et al., 2013). When assessing cocaine-associated memory by CPP, acute restraint stress before the test increased cue-induced cocaine seeking (Shinohara et al., 2018; Wada et al., 2020). This effect was mediated by α1 noradrenergic receptors in the mPFC (Wada et al., 2020). β-Adrenoreceptors in the PL were also shown to be involved in cocaine-memory retrieval (Otis et al., 2013). In this way, β-noradrenergic signaling inhibition during retrieval induced long-lasting cocaine-associated memory impairment and reversed cocaine-induced plastic changes in PL pyramidal neurons (Otis et al., 2018; Otis & Mueller, 2017). These findings point out the noradrenergic system in the mPFC as a key modulator of reward-learned behaviors, likely by inducing plastic changes in pyramidal neurons.

Noradrenergic system has been broadly studied in stress-induced fear conditioning and extinction tasks (Fitzgerald et al., 2015; Giustino & Maren, 2018). Favoring the notion of the LC as a heterogeneous nucleus with specific functions through different projection targets (reviewed by Chandler et al., 2019), Uematsu et al., (2017) showed that whereas LC-amygdala pathway participates in fear learning acquisition, LC-IL projection neurons are involved in fear learning extinction. Interestingly, LC pharmacogenetic activation induced fear reinstatement after extinction, accompanied by a decrease of IL firing (and an increase of PL firing) (Giustino et al., 2019). In this regard, it was suggested that NA in the mPFC could enhance or impair aversion learning depending on arousal states by acting in combination with amygdala function (Giustino & Maren, 2018; Giustino et al., 2020). Thus, it seems that an interplay between different subregions of the mPFC, amygdala, and the LC is essential for noradrenergic modulation of different phases of aversion-related memory.

There is still a lack of evidence on how NA in the mPFC modulates divergent pathways to induce approach or avoidance behaviors. Interestingly, NA was shown to enhance DA-induced activation of mPFC pyramidal neurons (Shinohara et al., 2020). Considering their shared mechanisms such as colocalized receptors, signaling pathways, and reuptake system (Devoto et al., 2020; Ranjbar-Slamloo & Fazlali, 2020; Xing et al., 2016), the crosstalk between NA and DA in the mPFC would be an interesting question for future studies assessing reward and aversion processing.

4.3 | Cholinergic modulation of mPFC

ACh is a key neurotransmitter in the mPFC which is involved in cognitive functions including attention (Guillem et al., 2011; Parikh et al., 2007), learning, and memory (Dalley et al., 2004; Hasselmo, 2006). Disruption of cholinergic neurotransmission in the mPFC has been linked with neurological disorders such as Alzheimer disease, schizophrenia, and substance use disorder (reviewed by Koukouli & Changeux, 2020).

ACh is released from boutons of axons that originate mainly from neurons of the basal forebrain (Mesulam, 2013) and acts by its G-protein coupled (muscarinic) or ligand-gated ion channels (nicotinic, nAChRs) receptors (Changeux, 2009; Gotti & Clementi, 2004; Wonnacott et al., 2005). Considering the broad innervation of the basal forebrain to virtually all the cortical areas and layers, a traditional view based on microdialysis and lesion studies sustained that ACh acts primarily by slow and diffused neurotransmission, supporting global brain states such as arousal. However, the use of advanced techniques with higher temporal resolution challenged that traditional view. Several studies showed that ACh focal and phasic release plays a key role on specific cognitive processing (Gritton et al., 2016; Hangya et al., 2015; Parikh et al., 2007; Sarter et al., 2014). However, it is still active debate about the importance of tonic/volume and phasic/focal cholinergic neurotransmission (Sarter & Lustig, 2020). In addition to the basal forebrain, the mPFC receives cholinergic projections from pontine nuclei (Bueno et al., 2019). Cholinergic interneurons involved in sustained attention were also described in the mPFC network (Obermayer et al., 2019).

Cholinergic innervation of the mPFC is topographically organized and layer segregated, with one population of basal forebrain neurons projecting to all layers and another projecting only to deep layers (Bloem, Schoppink, et al., 2014). Cholinergic receptors are also layer segregated (Poorthuis et al., 2013), pointing out the complex role of cholinergic modulation of the mPFC output. For example, α7 nAChRs are present in Layer 5 pyramidal neurons, which project to NAc, BLA, and PAG, but not in Layer 6 pyramidal neurons, which project to thalamic nuclei, including the PVT (Bloem, Schoppink, et al., 2014; Poorthuis et al., 2013). Noteworthy, ACh modulates mPFC pyramidal neurons, glutamatergic terminals, and also gabaergic interneurons (Poorthuis et al., 2013, 2014; Udakis et al., 2016), which are involved in disinhibitory circuits (Pi et al., 2013). These heterogenic

distributions highlight the complex role of cholinergic neurotransmission in the mPFC microcircuit. Electrophysiological studies in mice brain slices shown that α7 nAChRs can enhance glutamatergic and gabaergic activity in Layer 5 of the mPFC, although the net result was toward excitation of pyramidal neurons, that is, an increase of output activity (Poorthuis et al., 2013; Udakis et al., 2016).

How does ACh modulate mPFC top-down control of reward- and aversion-based behavior? ACh phasic release in the mPFC is involved in the detection of both reward- and aversion-related salient environmental cues, which are essential for guiding behavior (Gritton et al., 2016; Parikh et al., 2007). Moreover, it has been suggested that ACh neurons may encode reward-predictive value of sensory cues (Hangya et al., 2015; Leonor Teles-Grilo Ruivo et al., 2017). In support of this idea, pharmacological studies shown that mPFC α7 subtype of nAChRs are necessary for cue-induced cocaine seeking in a CPP task (Pastor et al., 2021). In addition to learned cues, basal forebrain cholinergic neurons showed a fast response to the presentation of innate rewarding (water) and aversive (air puff) stimuli (Hangya et al., 2015).

The results reviewed here suggest that layer-segregated cholinergic modulation of mPFC neurons projecting to specific subcortical areas—primarily involved in reward or aversion—could be participating in attention-guided approach or avoidance behaviors. However, there are several questions regarding mPFC modulation by ACh which remain unanswered. For example, disinhibitory circuits in the mPFC are involved in fear memory expression (Courtin et al., 2014). Moreover, basal forebrain ACh neurons modulate disinhibitory circuits in the auditory cortex (Guo et al., 2019) and the amygdala (Krabbe et al., 2019) controlling associative memory of salient aversive events. Does this type of stimuli processing—that is, basal forebrain acting on disinhibitory circuits to modulate reward or aversive memories—apply for the mPFC microcircuitry? On the other hand, ACh could be regulating the role of other neuromodulators such as DA or 5HT. In this way, cocaine-seeking induced by reward-associated cues was impaired by the antagonism of dopaminergic (Shinohara et al., 2017) or cholinergic (Pastor et al., 2021) receptors in the mPFC. Despite it was shown that ACh modulates DA release in the PFC (Jaffé & Hernández, 1989; Livingstone et al., 2009), it remains unknown if those modulatory systems act together to control reward-based behavior.

4.4 | Serotoninergic modulation of the mPFC

5HT participates in global brain state changes such as transition from sleep to wakefulness (Hobson & Pace-Schott, 2002) and is highly involved in attention, social interaction, and memory processing (Morici et al., 2018). Disruption of 5HT signaling in the mPFC induces neuropsychiatric disorders such as schizophrenia, depression, anxiety, and substance use disorders (Aznar & Hervig, 2016). However, how 5HT modulates mPFC function is not clear, and thus, therapeutic strategies modifying 5HT system are not always effective.

The mPFC receives 5HT inputs from the dorsal raphe (and in a lesser extent the medial raphe) nuclei (Van Bockstaele et al., 1993; Vertes et al., 1999). It is modulated by several types of 5HT receptors, which are expressed in a layer-segregated manner across all mPFC subregions, primarily in pyramidal neurons (Leiser et al., 2015; Price et al., 2019; Santana & Artigas, 2017). As discussed for other subcortical structures, dorsal raphe has subpopulations of neurons with specific targets which—when activated—entail different behavioral outputs. In this way, Ren et al., (2018) showed that dorsal raphe 5HT neurons projecting to orbitofrontal cortex are activated by reward, inhibited by punishment, and promote active coping behavior in a forced swimming test. In the same study, the authors found that dorsal raphe to amygdala projecting neurons are activated by both reward and punishment and promote anxiety behaviors. In addition, optogenetic activation of dorsal raphe 5HT-VTA projecting neurons induced preference whereas their inhibition induced aversion for a conditioned context (Nagai et al., 2020; Wang et al., 2019).

Despite the gap of knowledge about the role of raphe nuclei projections to the mPFC in reward and aversion processing, mPFC 5HT has been shown to be involved in both reward and aversion tasks, with differential effects depending on the mPFC subregion and the type of receptor targeted. In this way, pharmacological experiments showed that reinstatement of cocaine-seeking behavior after extinction was attenuated by 5HT-2A blockade (Pockros et al., 2011) and by 5HT-2C activation (Pentkowski et al., 2010). In the mPFC, Mocci et al., (2014) showed that pyramidal neurons projecting to the NAc are modulated by excitatory 5HT-2A receptors, adding to the role of mPFC 5HT in the modulation of reward-based behavior. On the other hand, exposure to a conditioned aversive context increases mPFC 5HT levels (Yoshioka et al., 1995) and 5HT receptors in the PL—but not the IL—are involved in the expression of fear conditioning (Almada et al., 2015).

As we mentioned in previous sections, 5HT interaction with other neuromodulators such as DA (Bortolozzi et al., 2005) or ACh (Sparks et al., 2018) is probably a key point to understand overlapping/opposing actions between neuromodulatory systems which will improve the understanding of their role on mPFC control.

4.5 | Modulatory systems in the mPFC: Concluding remarks

The analysis of the studies reviewed in these sections rises several questions that should be addressed in future studies

to increase our understanding of the neuromodulatory interplay in the mPFC. In an ever-changing environment, our brain must constantly adjust arousal and attention to different kinds of sensory stimuli. How do modulatory systems synergize to shape global brain states which may influence the way the mPFC process sensory information to drive behavior? Moreover, our brain must compute prediction errors to learn about rewarding and aversive experiences which will guide our behavior. Are volume and focal neurotransmission working together to modulate global brain states and to process reward- and aversion-related sensory stimuli?

It is evident from the above reviewed studies that the mPFC plays an essential role on our choices toward approaching or avoiding certain stimuli or contexts. Importantly, reward and aversion are not absolute entities but the ends of a continuum spectrum of stimuli which compete for inducing an approach or avoidance behavioral output. Neuromodulatory systems have complex reciprocal connections between them and with the mPFC. Moreover, they can modify neurotransmitter release at the axon terminal level. These features make bottom-up systems crucial to induce a tuned control of mPFC neurons for regulating the continuum spectrum of possible behavioral outputs. However, how do different neuromodulatory systems combine to shape mPFC role on reward- and aversion-induced behavior is an open question which should be more deeply assessed for a better understanding of neocortical function. Combining modern circuit, genetic, and imaging techniques with pharmacological tools will help to understand the modulatory coding of DA, NA, ACh, and 5HT inputs to the mPFC and their overlaps/dissociations. This will lead to the development of better strategies for neuropsychiatric diseases related to abnormal reward- or aversion-based learning.

5 | CONCLUSIONS

In this review, we summarized anatomical, pharmacological, behavioral, and functional evidence showing that bottom-up neuromodulation of the mPFC is essential for the top-down control of reward- and aversion-based behavior. Approach and defensive behaviors are often adaptive. However, in animals and humans, a lack of control of reward or aversion processing may induce a pathologic expression of those behaviors. Thus, comprehending the role of the mPFC in reward and aversion is not only an important goal on its own right but may also shed light on understanding the consequences of an altered prefrontal function in psychiatric diseases such as anxiety and substance use disorders. According to the DSM-V, a clinical hallmark of substance use disorder includes the use of a drug despite its potential harmful consequence (American Psychiatric Association, 2013). As we discussed above, the mPFC is essential for decreasing the frequency of a behavior which brings a harmful consequence and the effectiveness of mPFC function depends on its correct neuromodulation and subcortical targeted brain areas. On the other hand, fear generalization is a key feature of anxiety disorders (Dymond et al., 2015). In the same way, a correct neuromodulation of the mPFC may allow the correct flow of information to subcortical areas to allow an approach behavior when avoidance is not necessary. Thus, understanding the way in which DA, NA, ACh, and 5HT converge in the mPFC to modulate reward and aversion control might provide valuable pharmacological targets to improve therapy strategies for the treatment of some mental disorders.

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CONFLICT OF INTEREST

The authors declare no conflict of interest. The funders had no role in data collection and interpretation or the decision to submit the work for publication.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable as no original data were created or analyzed in this study.

ORCID

Verónica Pastor https://orcid.org/0000-0002-5404-5808

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