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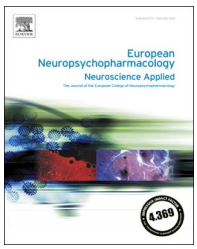

REVIEW

Divergent prefrontal dopaminergic mechanisms mediate drug- and fear-associated cue extinction during adolescence versus adulthood

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Abstract
Cue-associated learning is vital to guiding behaviour for survival. Adolescence represents a key developmental stage for perturbations in cue-related learning, including a characteristic deficit in cue extinction learning. The present review summarizes evidence from animal and human literature that cue extinction is critically mediated by prefrontal dopamine, a system that undergoes dramatic reorganization during adolescence. We propose that extinction learning and memory is governed by a developmentally dynamic balance of dopamine receptors in the prefrontal cortex, which changes across adolescence into adulthood. This is contrary to the previous idea that extinction deficits during adolescence reflect inefficiency in the same neural circuitry as adults. This leads to proposal of the novel theory that cue extinction involves divergent prefrontal dopaminergic mechanisms depending on the age of extinction.

1. Introduction

Cues in our environment can act as powerful triggers for guiding behaviour. For example, when a cue is repeatedly paired with a particular stimulus, such as a mild electric shock or a drug of abuse, the cue becomes associated with

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that stimulus. In this way, the cue by itself can elicit an emotional or physiological response, a process known as *cue conditioning*. This process can trigger behavioural patterns such as fear or avoidance in the case of an aversive cue, or craving in the case of a rewarding stimulus. However, just as we can learn to associate a cue with a certain experience, we can also learn to suppress our conditioned response to a cue. When a cue is repeatedly presented alone, we learn that the cue no longer predicts the associated stimulus, a process known as *cue extinction* (Pavlov, 1927). Through cue extinction, our emotional or physiological response to the cue is inhibited, decreasing over repeated exposure to the cue by itself. Critically, adolescence represents a period of perturbed cue extinction learning, compared to both younger and older age groups (Baker and Richardson, 2015; Kim et al., 2011; Pattwell et al., 2013). Therefore, understanding the neural mechanisms of cue extinction across development represents a key area for neuroscientific investigation.

A growing body of evidence indicates that cue extinction during both adolescence and adulthood involves the prefrontal cortex (PFC) (Baker and Richardson, 2015; Kim et al., 2011; Pattwell et al., 2013). This is consistent with the well-established role of the PFC in coordinating executive function and affective regulation (Fuster, 2015; Miller and Cohen, 2001). However, natural maturational changes occurring in the PFC during adolescence mean that the specific mechanisms of extinction in the PFC may be different during this period compared to other ages. One system undergoing reorganization in the PFC during adolescence is the dopamine system (Kim et al., 2017). The present review will therefore explore the role of prefrontal dopamine in cue extinction across adolescent development. In addition to summarising evidence for the importance of prefrontal dopamine in cue extinction during adulthood, we review recent evidence for this system in adolescent cue extinction. We then propose the novel theory that prefrontal dopamine is differentially involved in cue extinction learning across maturation.

2. Prefrontal dopamine and extinction learning in adulthood

Extensive evidence suggests that extinction is controlled by the medial PFC (mPFC), a brain region conserved across humans and rodents (Gass and Chandler, 2013; McNally, 2014; Millan et al., 2011; Myers and Carlezon, 2010). Dominant neural models state that extinction of drug seeking involves glutamatergic outputs from the infralimbic cortex (IL) of the mPFC to the nucleus accumbens (NAc) shell (LaLumiere et al., 2010; Peters et al., 2008). In the case of fear extinction, the IL sends excitatory projections to the local gamma-aminobutyric acidergic (GABAergic) inhibitory cells in the basolateral nucleus (BLA), and/or the intercalated cells (ITCs) of the amygdala, which subsequently inhibit the central amygdala (Herry et al., 2006; Knapska and Maren, 2009; Rosenkranz and Grace, 2002). By comparison, the prelimbic cortex (PL) of the mPFC is thought to mediate the expression of drug-seeking and conditioned fear via outputs to the NAc core and BLA, respectively. While some data suggest that the IL and PL can also act in concert, at least under some conditions, it is widely accepted that the PL and IL most often code for opposing behaviors in terms of drug-seeking and conditioned fear (Giustino and Maren, 2015; Peters et al., 2009).

A key role for prefrontal dopamine in extinction learning is consistent with evidence that dopamine strongly mediates information processing (Ridderinkhof et al., 2004). Dopamine exerts its effects in the cortex via five G protein-coupled receptors (GPCRs), which are broadly divided into two groups: the dopamine 1-like receptors (dopamine 1 receptor [D1R] and D5R) and the dopamine 2-like receptors (D2R, D3R, D4R). Being GPCRs, activation of D1R and D2R is able to stimulate a range of second messenger pathways and effector proteins (Seamans and Yang, 2004a). However, each receptor class stimulates different second messenger pathways and effector proteins, which often lead to opposite effects (Tritsch and Sabatini, 2012). Specifically, activation of D1 receptors causes excitation in the postsynaptic cell through activation of G proteins positively coupled to adenylyl cyclase, which results in the production of cyclic adenosine monophosphate (cAMP) and activation of protein kinase A, as well as phosphorylation of dopamine and cAMP-regulated phosphoprotein-32 (DARPP-32). This produces phosphorylation of K+ channels and decreased conductance, and thereby enhances the excitability of the postsynaptic cell (Tritsch and Sabatini, 2012). Thus, when dopamine binds and activates D1R, it can inhibit PFC through excitation of inhibitory interneurons. Conversely, activation of D2R triggers a signal cascade that ultimately decreases GABA currents postsynaptically, decreasing the inhibition of PFC networks (Trantham-Davidson et al., 2004). Activation of D1Rs has been shown to follow an inverted U-shape function in working memory, such that either too little or too much activation can disrupt performance (Goldman-Rakic et al., 2000; Seamans and Yang, 2004a). The role of D2Rs in working memory is less clear (Jay, 2003), though prefrontal D2R activation is generally associated with decreased cAMP synthesis and inactivation of N-methyl-D-aspartate receptor (NMDAR) (Seamans and Yang, 2004a). Further, D1R signaling is known to facilitate long term potentiation (LTP), whereas D2R signaling is associated with long term depression (LTD) (Sheynikhovich et al., 2013).

In the PFC, dopamine exerts its effects via D1Rs and D2Rs expressed primarily on parvalbumin-positive fast-spiking interneurons (Gorelova et al., 2002; Le Moine and Gaspar, 1998). However, both D1Rs and D2Rs are also expressed on prefrontal pyramidal neurons, allowing dopamine to play both direct and indirect roles on prefrontal output (Santana et al., 2009). Thus in addition to modulating information processing within the PFC, dopamine is also important for gating incoming sensory information and directing output from the PFC to other brain regions, including the NAc and amygdala (Abraham et al., 2014). Given the importance of PFC output to these regions for extinction, it makes sense that studies are beginning to highlight PFC dopamine signaling in both fear- and drug-related extinction.

Indeed, presentation of a cue previously associated with a natural reward or a footshock increases dopamine release in the PFC of adult rats (Feenstra et al., 2001; Milella et al., 2016; Wędzony et al., 1996). Similarly, presentation of drug-related cues induces robust dopamine release in the PFC in humans with cocaine use disorder (Milella et al., 2016).

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