CHAPTER TWO

Neural systems for aversively motivated behavior

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Abstract

The neural basis of motivation is supported by brain systems that are integral in behaviors that maximize positively valued stimuli and minimize aversive stimuli. This article focuses on brain systems involved in minimization of aversive stimuli, which are extensively described by a substantial history of research on behaviors in nonhuman animals that are motivated by aversive stimuli. Such research strongly delineates a neural circuitry involving amygdala and striatum sub-nuclei that are modulated by regions of prefrontal cortex. Neuroimaging research on behaviors motivated by aversive stimuli in humans has confirmed the importance of homologous systems in humans, and allowed some understanding of the relation of these circuits to distinct behavioral responses and to clinical issues such as anxiety. We organize our review of this research around three important conceptual observations. First, active avoidance behaviors are distinguishable from passive avoidance behaviors in terms of both neural circuitry and motivational and affective consequences. Second, the perception of control over stimuli is critical for active avoidance behaviors, and influences brain systems for avoidance as well as subsequent behavior toward motivational stimuli. Third, avoidance behaviors may be adaptive in many

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situations but can become excessive or maladaptive in other situations. Knowledge about the neural circuitry underlying active avoidance provides an important path in understanding how avoidance behaviors are maintained and how they may change, and form a foundation for studying motivation and clinical issues such as anxiety.

Motivation is commonly understood as the purpose or direction of a course of action, and the effort or energy one is willing to put forth to complete the course of action (Elliot, 2006). Motivations can be multi-faceted, and distinguishable by the behaviors they cause. For example, an employee may have multiple motivations such as wanting to minimize the unpleasantness of a meeting, or wanting to maximize pleasant time with family. The same motivation to minimize unpleasantness of a meeting might lead to distinct behaviors. That is, one employee might actively avoid the meeting by giving an excuse and leaving, but another employee might passively stay in place (hoping they are not compelled to participate). These different actions might be determined by various factors, such as the employee's perception of control in their situation (i.e., the belief that they can take an action to avoid the meeting). The actions might also be determined by habits. For example, an employee might be in the habit of always making excuses to avoid weekly meetings, to the point that they do so even on a day when the meeting is canceled. These examples of behavior are chosen because they illustrate three important observations about aversively motivated behavior: (1) responses to aversive stimuli can be conceptualized as active or passive responses, depending on whether an action attempts to avoid (or escape/reduce) an aversive outcome, and these responses involve distinct neural pathways; (2) the perception of control in an aversive situation can influence the neural pathways for active and passive responses, suppressing passive responses and enhancing active responses; and (3) avoidance behaviors can become insensitive to changes in the aversive outcomes they attempt to avoid, and excessive avoidance behaviors may share neural substrates involved in the maintenance of habits.

This article reviews research that links aversively motivated behaviors to the function of brain regions where interconnected structures in the amygdala, striatum, and medial prefrontal cortex (mPFC) play prominent roles. Research on aversively motivated behavior in rodents provides a detailed understanding of these neural circuits, therefore, this review describes foundational research in rodent models as well as research on human behavior that generally shows consistency in the neural circuits underlying aversively

motivated behavior (Fenster, Lebois, Ressler, & Suh, 2018; Mobbs & Kim, 2015; Phelps & LeDoux, 2005; Quirk & Beer, 2006; Roberts & Clarke, 2019). Importantly, the three general observations described above appear consistent across rodent and human models: active responses are distinguished from passive responses, the perception of control influences neural pathways for aversively motivated responses, and avoidance behaviors can become insensitive to the outcomes they intend to avoid. This article focuses on neural systems underlying aversively motivated behaviors for two primary reasons. First, the distinction between positively motivated approach behaviors and aversively motivated avoidance behaviors is central to the study of motivation (Elliot, 2006) and a rich literature on the neural circuits underlying aversive avoidance behaviors in nonhuman animals provides a strong foundation for understanding neural systems underlying aversively motivated behavior in humans (Diehl, Bravo-Rivera, & Quirk, 2019; LeDoux, Moscarello, Sears, & Campese, 2017). Second, these aversive motivational systems are critical for understanding important clinical issues in humans. That is, increased understanding of neural circuitry underlying aversive avoidance behaviors has provided hypotheses concerning dysregulated neural systems in anxiety (LeDoux & Pine, 2016; Urcelay & Prével, 2019; White et al., 2017), obsessive compulsive disorder (Gillan et al., 2014), post-traumatic stress disorder (Fenster et al., 2018), and addiction (Fattore, Piras, Corda, & Giorgi, 2009; LeDoux et al., 2017).

1. Neural systems underlying responses to aversive stimuli: Passive and active defensive behaviors

An aversive stimulus is an unpleasant negative valence event or object, such as a painful electric shock, a signal of danger, or a disliked food. In nonhuman animal research, aversive stimuli are identified as those that elicit behavior aimed at reducing or removing the stimulus (when reduction or removal is possible). In human research, aversive stimuli can be identified in the same way or by the subject's explicit identification of a stimulus as negative valence. Variations of aversive paradigms have been used extensively along with lesion, neuronal recording, and fiber tracing methods to identify the flow of signals between brain regions that are necessary for typical behavioral responses to aversive stimuli (Davis, 1992; Davis, Walker, Miles, & Grillon, 2010; Diehl et al., 2019; Duvarci & Pare, 2014; Haaker et al., 2019; LeDoux et al., 2017; Machado, Kazama, & Bachevalier, 2009).

Here, we focus on paradigms that measure responses to an aversive stimulus, such as an electric shock or a signal that predicts electric shock. Specifically, we review neural circuitry underlying responses that can be categorized as passive behaviors (i.e., no overt action to avoid or escape an aversive stimulus) or active behaviors (i.e., action taken to escape or avoid an aversive stimulus or its consequences) in response. The evidence we review shows that aversive motivational cues (a) engage distinct passive or active avoidance responses that rely on distinct neural circuits in which amygdala and striatum sub-regions are integral, (b) prompt arbitration between passive and active avoidance responses that depends in part on factors within amygdala sub-regions, and (c) engage neural circuitry that is generally comparable between humans and nonhuman animals, with a greater level of anatomical detail in rodent research and greater level of behavioral/psychological complexity in human research.

1.1 Passive responses to aversive stimuli in nonhuman animals

A substantial history of research using Pavlovian conditioning with aversive stimuli has detailed the neural mechanisms that are involved in generating the conditioned response. These neural mechanisms have been extensively studied in rodents, where a neutral stimulus (often an auditory tone) becomes a conditioned stimulus (CS) after repeatedly overlapping with a unconditioned aversive stimulus (US), such as an inescapable electric shock to the foot. In rodents, freezing behavior is typically observed as part of the unconditioned response to an inescapable aversive US (Diehl et al., 2019; LeDoux et al., 2017; Pliota et al., 2020). After repeated pairings of CS with US, animals will express a conditioned response to the CS by itself. That is, they will freeze in response to the tone in absence of shock, as part of a conditioned response that includes endocrine and autonomic changes, such as heart rate changes. This conditioned response can be considered a species-specific defensive response to the threat signaled by the CS, though there are similarities across different species (Haaker et al., 2019). Furthermore, conditioned responses to inescapable threats can be generally characterized as passive (Forcelli et al., 2016; Machado et al., 2009; Moscarello & Hartley, 2017), in that there is no overt action to flee or avoid the threat, and the response prevents the animal from engaging in other valued actions, such as reward seeking (Diehl et al., 2019; Forcelli et al., 2016). A common factor in these learned conditioned responses to inescapable threats is the encoding of an association between the CS and US. This association relies on changes in CS-evoked neuronal activity in sub-nuclei of the amygdala as the initially

neutral stimulus acquires aversive value and the conditioned response is generated by the CS.

The lateral nucleus and central nucleus of the amygdala are necessary for the acquisition of a conditioned response to inescapable threat. Specifically, the lateral amygdala receives CS and US information from sensory and contextual processing (hippocampus) regions. During acquisition, populations of lateral nucleus neurons increase activity in response to the conditioned stimulus onset, enabled by local cellular and molecular changes (Duvarci & Pare, 2014; LeDoux et al., 2017; Maren, 2005; Rodrigues, Schafe, & LeDoux, 2004). Through direct and indirect (through basal and intercalated nuclei of the amygdala) connections this signal flows to the central nucleus of the amygdala. This signal can be considered an aversive value signal (Morrison & Salzman, 2010; O'Neill, Gore, & Salzman, 2018; Paton, Belova, Morrison, & Salzman, 2006), which is received in the central nucleus where the conditioned response is effected via projections to midbrain nuclei that control behavioral responses (e.g., freezing), and hypothalamic and brainstem sites that control endocrine and autonomic components of the conditioned response (Diehl et al., 2019; Duvarci & Pare, 2014; LeDoux et al., 2017). Thus, sensory and contextual information flows first to the lateral nucleus of the amygdala, which creates the association between CS and US. After this association is learned, the CS alone generates a signal in the lateral nucleus that is conveyed to the central nucleus of the amygdala, and the central nucleus signal promotes the passive conditioned response, such as freezing in rodents (Diehl et al., 2019; LeDoux et al., 2017; Roberts & Clarke, 2019). Once this response to the CS is established, it is long lasting (Pliota et al., 2020). That is, even after extinction (CS presented without the aversive US until the conditioned response is no longer evoked), the CS-US associative memory remains and the conditioned response can be spontaneously recovered by a change of context, re-exposure to the US, renewed CS-US pairing, or passage of time (Bouton, 2004). Critically, this pathway conveying a passive response to a threat is evoked in a situation where the animal has no avenue of control over the unconditioned stimulus. When the possibility of avoiding a threat exists, a separable pathway involving the amygdala becomes important.

1.2 Active avoidance responses to aversive stimuli in nonhuman animals

The response to an aversive CS changes if a simple variation is made to the paradigm by creating an avenue to avoid or escape from the aversive US. In signaled active avoidance paradigms, an animal perceives a cue (e.g., a tone)

that predicts an upcoming aversive outcome (e.g., painful shock) and it can perform an active response to avoid the aversive outcome. This active response could be to move to a safe area or press a lever, which would avoid the aversive outcome and in some versions of the paradigm terminate the cue. This active response is triggered by the CS, after the individual has learned that the CS predicts the aversive US. Consequently, the CS is better described as a warning signal in this paradigm, although it can be identical in sensory features to a CS in a passive conditioning paradigm (Diehl et al., 2019). The critical stages of learning in this signaled active avoidance paradigm are thus: (a) learning that the CS/warning signal predicts the US; (b) learning the active response that terminates the US; and then (c) learning to enact the active response once the CS/warning signal is present in order to avoid the US entirely (Diehl et al., 2019; LeDoux et al., 2017). In the same manner that the lateral nucleus of the amygdala is integral to learn the association between the CS and the US in a passive conditioning paradigm, this same region is integral in learning the similar association between the CS/warning signal and the US in the first stage of signaled active avoidance (Diehl et al., 2019; LeDoux et al., 2017). Next, the individual discovers the active response to terminate the US, which is triggered by the aversive US itself. The basolateral complex of the amygdala (consisting of basal and lateral sub-nuclei) is integral in such escape behaviors, regardless of CS/warning signal presence (Terburg et al., 2018). Finally, learning progresses to the point that the active response is triggered by the CS/warning signal before US onset and the individual actively avoids the aversive US before its onset. This active response triggered by the CS/warning signal relies on a signal communicated from the lateral nucleus to the basal nucleus of the amygdala. This signal carrying information about the CS/warning signal is then conveyed on projections to the ventral striatum (including nucleus accumbens), which in turn controls the active avoidance response (Diehl et al., 2019; LeDoux et al., 2017; Sangha, Diehl, Bergstrom, & Drew, 2020). Thus, critical neural signals in active avoidance involve first the lateral amygdala activity carrying information about the CS/warning signal and its association to the US, then conveyance of that signal to the ventral striatum.

Importantly, the pathways discussed for passive and active avoidance responses share a common component: lateral amygdala activity conveying information about the CS/warning signal that predicts the aversive US. But both passive and active behaviors cannot be enacted, thus the pathways (and behaviors) compete. Indeed, failures for individual rodents to learn an active avoidance response can be attributed to overuse of passive responses

(Choi, Cain, & LeDoux, 2010; Galatzer-Levy et al., 2014), and these failures can be rectified by damage to the central amygdala (the part of the circuit unique to passive reactions) (Lázaro-Muñoz, LeDoux, & Cain, 2010). Even in individuals that successfully learn the active avoidance response typically express passive responses before learning the active response (Diehl et al., 2019). The arbitration between pathways to passive and active avoidance behaviors is controlled in part by factors within amygdala (Fadok et al., 2017; Gozzi et al., 2010), but is also influenced by signals from prefrontal cortex that may take contextual factors into account, including the level of control that the individual has over the aversive outcome (Amat et al., 2005; Diehl et al., 2019; LeDoux et al., 2017). The balance between passive and active avoidance behaviors motivated by aversive stimuli is a key area of research to understand adaptive and maladaptive patterns that may be important in understanding fear, anxiety, and disorder in humans.

1.3 Passive and active avoidance responses in humans

The basic neural mechanisms of passive and active avoidance responses to aversive motivational stimuli are generally consistent across research in rodents, nonhuman primates, and humans. Anatomical precision to localize pathways within sub-regions of amygdala (i.e., lateral, basal, and central nuclei) is difficult in lesion patient and neuroimaging methods used in humans. However, key elements of the distinction highlighted here between passive and active avoidance pathways have been supported by human research. For example, functional magnetic resonance blood-oxygen-level-dependent (fMRI BOLD) signal in amygdala is correlated with signal in ventral striatum during active avoidance behaviors motivated by aversive stimuli, such as making a response to avoid monetary loss or shock (Collins, Mendelsohn, Cain, & Schiller, 2014; Delgado, Jou, Ledoux, & Phelps, 2009). Though fMRI does not establish direction of information flow, this amygdala-striatum signal correlation is consistent with information about a possible aversive outcome being conveyed from amygdala to ventral striatum similarly to the pathway established in nonhuman animals. Furthermore, active avoidance increases fMRI BOLD signal in ventral striatum, whereas passive responses to aversive stimuli coincide with decreases in ventral striatum signal, suggesting ventral striatum is involved in active responses to aversive stimuli (Levita, Hoskin, & Champi, 2012) similar to its role identified in rodent research. The amygdala is necessary for expression of conditioned responses to aversive stimuli in

humans (Phelps & LeDoux, 2005) and there is work showing that these conditioned responses (measured by pupil dilation, skin conductance, potentiated startle reactions, or reduced body movement) can be considered analogous to passive responses in nonhuman animals (e.g., reduced body movement in humans resembles freezing in rodents) (Haaker et al., 2019).

While anatomical and cellular/molecular detailed knowledge of these circuits in humans is less than in nonhuman animals, the foundational knowledge provided by nonhuman animal research affords new opportunities for investigations. Using functional neuroimaging in humans, studies have begun to examine the greater complexity, measurement opportunities (e.g., emotional self-report), and different time scales of motivational states and behavior that are possible in humans. For example, in the conditioning and active avoidance paradigms described here, the inescapable aversive CS-elicited state may be characterized as fear, but when a similar cue indicates a possible aversive outcome with greater physical or temporal distance it may be characterized as anxiety, which involves regions beyond the amygdala-ventral striatum circuit described thus far (Shackman & Fox, 2016). Furthermore, this research allows for identification of dysregulated components of the neural circuitry underlying aversively motivated passive and active avoidance responses, which may contribute to disorder in humans (Gillan et al., 2014; LeDoux & Pine, 2016; Mobbs & Kim, 2015; White et al., 2017). In particular, an important area of research examines how neural activity arbitrates between passive and active avoidance responses, which we discuss in the next section.

2. Perceived control alters aversively motivated behavior via medial prefrontal modulation

Earlier we distinguished between examples of an employee who actively avoids the unpleasant meeting vs an employee who passively remains in place. The level of control that the employee perceives in the situation is important in determining these distinct responses. For example, an employee who has prior experiences of successfully avoiding or escaping meetings would perceive a high level of control in situations involving unpleasant meetings. An individual who has a high level of perceived control believes their actions will result in a desired outcome and is likely to actively cope with an aversive stimulus rather than passively respond. This perception of control can be conceptualized as a difference between individuals (Rotter, 1966), as a cognitive set in a situation (Bandura & Wood, 1989),

or as a dynamic interpretation of agency based on an individual's history of contingency between actions and desired outcomes in different situations (Moscarello & Hartley, 2017; Wang, Yang, & Delgado, 2021).

In situations that reliably elicit a passive response, such as freezing in response to aversive Pavlovian cues, an individual has no avenue to control the anticipated aversive outcome. In situations that reliably produce active avoidance responses there is an action that controls the aversive outcome. The perception of control is formed through experiences between actions and desired outcomes and can be specific to a situation such as the active avoidance paradigm, but controllable and uncontrollable aversive experiences also have enduring effects that influence perception of control in varying situations (Huys & Dayan, 2009; Ly, Wang, Bhanji, & Delgado, 2019; Moscarello & Hartley, 2017). In this section, we discuss two ways in which perceived control over aversive outcomes may have enduring effects. First, the experience of control in one situation alters responses to aversive stimuli in future situations (Moscarello & Hartley, 2017). Second, the perception of control alters appetitively motivated behaviors that are normally suppressed in situations where aversive outcomes are possible (Diehl et al., 2019). From the detailed understanding of amygdala and striatum sub-regions that implement passive or active responses to aversive stimuli, we can build an understanding of the enduring motivational effects that result from the experience of control over aversive stimuli (see Fig. 1).

2.1 Perceived control decreases passive responses to aversive stimuli

In the signaled active avoidance paradigm discussed above, individuals who learn the active avoidance response must transition from a passive to an active response to the CS/warning signal. The passive response is present in a state where the individual is aware of the contingency between CS/warning signal and the aversive outcome, but has no experience of contingency between an action and a desired outcome. The experience of a desired outcome (termination of the aversive outcome) after performing the active response provides the contingency between action and outcome that can increase the level of perceived control in the situation (Diehl et al., 2019). With the increase in perceived control, the passive response evoked by the CS/warning signal is suppressed (Diehl et al., 2019; LeDoux et al., 2017). This transition relies on integrity of medial prefrontal cortex (mPFC), specifically the infralimbic cortex in rodents, which provides input to the amygdala that suppresses passive conditioned responses to aversive

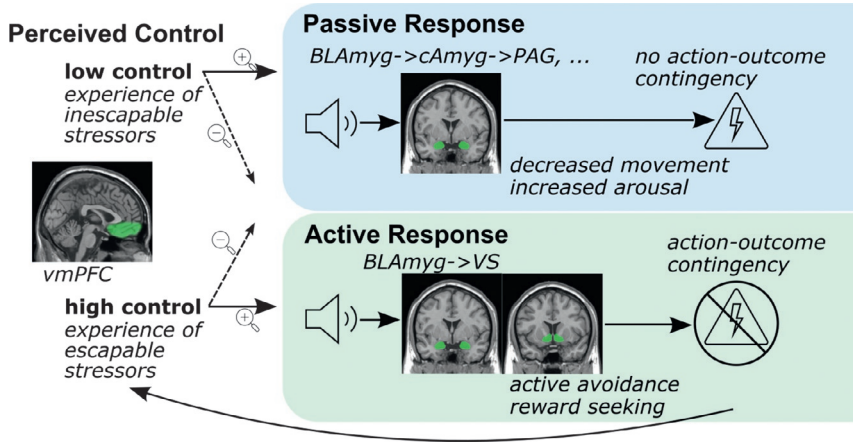

Fig. 1 Perceived control influences pathways for passive vs active responses to aversive stimuli. Ventromedial prefrontal cortex (vmPFC) is integral for perceiving control over aversive stimuli, and influences whether a cue (e.g. a tone) associated with an aversive outcome (e.g., a shock) evokes a passive response via a pathway from basal and lateral amygdala (BLAmyg) to central amygdala (cAmyg) to periaqueductal gray (PAG) and other sites, or an active response via a pathway from BLAmyg to ventral striatum (VS).

cues (Bravo-Rivera, Roman-Ortiz, Brignoni-Perez, Sotres-Bayon, & Quirk, 2014; Martinez et al., 2013; Moscarello & LeDoux, 2013). The infralimbic cortex is homologous to the ventromedial prefrontal cortex (vmPFC) in humans (Bhanji, Smith, & Delgado, 2016; Delgado et al., 2016; Heilbronner, Rodriguez-Romaguera, Quirk, Groenewegen, & Haber, 2016), which is similarly involved in inhibiting passive responses to aversive stimuli in human fMRI research (Hartley, Gorun, Reddan, Ramirez, & Phelps, 2014; Schiller & Delgado, 2010; Schiller, Levy, Niv, LeDoux, & Phelps, 2008; Wanke & Schwabe, 2020).

The experience of control not only suppresses passive responses in repetitions of the same aversive situation, but can also suppress passive responses in subsequent distinct aversive situations. Lack of control induced by exposure to inescapable stressors (e.g., inescapable aversive tail shocks in rodents) is well known to cause a phenomenon known as learned helplessness, which includes increased passive responses to aversively conditioned stimuli (Maier, 2015; Maier & Seligman, 1976, 2016). On the other hand, the experience of control over identical stressors (e.g., escapable aversive tail shocks) decreases passive responses to aversively conditioned stimuli, compared to an unstressed condition (Maier, 2015). Furthermore, the experience of control can block future effects of uncontrollable stress, an effect known as

"immunization" against learned helplessness phenomena (Maier, 2015; Maier & Seligman, 1976). Importantly, these effects are enduring, lasting across developmental stages (e.g., rodent adolescence to adulthood; (Kubala, Christianson, Kaufman, Watkins, & Maier, 2012)). Similar to the mechanism for suppression of passive responses in signaled active avoidance, these effects of control are reliant on signaling from the infralimbic area of rodent mPFC (Amat et al., 2005; Maier, 2015). Specifically, infralimbic cortex is necessary for detecting control over aversive events and projects to amygdala to inhibit passive responses to aversively conditioned stimuli (Baratta, Lucero, Amat, Watkins, & Maier, 2008; Sierra-Mercado, Padilla-Coreano, & Quirk, 2011). Projections from infralimbic cortex to the dorsal raphe also carry effects of control such that the experience of control over aversive stimuli inhibits the increase in dorsal raphe serotonin signaling that contributes to learned helplessness and passive responses to aversive stimuli (Maier, 2015).

Another situation that involves the suppression of passive responses to aversively conditioned stimuli is the case of extinction of aversively conditioned responses. When a CS that previously predicted an aversive outcome is then repeated without the aversive outcome, the passive response to the aversive CS is eventually extinguished over time, with this process similarly depending on a signal pathway from infralimbic cortex to amygdala (Sangha et al., 2020). After extinction, the passive response to the aversive CS can still show spontaneous recovery with a novel context, re-exposure to the US, renewed CS-US pairing, or passage of time (Bouton, 2004). The prior experience of control over an aversive outcome facilitates extinction and inhibits spontaneous recovery of the passive aversive conditioned response. These effects also rely on signaling from the infralimbic cortex to amygdala (Baratta et al., 2007, 2008). Thus, research in rodents suggests that increasing the experience of control has consistent effects that reduce passive responses to aversive stimuli and rely on mPFC.

These effects of control appear to be consistent in research paradigms adapted for humans. The prior experience of control over aversive outcomes (escapable compared to equivalent but inescapable shocks) increases the perception of control, facilitates extinction, and inhibits spontaneous recovery of aversively conditioned passive responses (measured by skin conductance changes; Hartley et al., 2014, Hartley, Coelho, Boeke, Ramirez, & Phelps, 2019; Wanke & Schwabe, 2020). Consistent with the importance of mPFC to amygdala signals demonstrated in rodent research, correlation between vmPFC and amygdala fMRI BOLD during extinction is increased in

humans who have had prior experience of control over the aversive outcome (Wanke & Schwabe, 2020). Cognitive regulation over an aversive cue (e.g., focusing on calming features of an aversively conditioned cue) can be considered a form of control over one's own passive response (though not over the aversive outcome) and similarly involves vmPFC signal increases and amygdala signal decreases (Delgado, Nearing, LeDoux, & Phelps, 2008). Furthermore, factors that may decrease perceived control, such as a prior acute stressor, decrease the effectiveness of cognitive regulation of aversively conditioned responses (Raio & Phelps, 2015) and impair the learning of aversive CS-US associations that have changed (Raio, Hartley, Orederu, Li, & Phelps, 2017). Without consideration of prior control, extinction or reversal of CS contingencies can reduce passive responses to aversive stimuli in humans. This reduction in passive responses involves increased vmPFC and decreased amygdala responses to aversive stimuli (Schiller & Delgado, 2010). This vmPFC association with the reduction of aversively conditioned responses supports an interpretation that vmPFC provides a signal that a situation is safe, which can be increased when individuals perceive control over aversive outcomes in the environment (Harrison et al., 2017; Sangha et al., 2020; Schiller et al., 2008). This body of research suggests that the vmPFC is important for detecting control and consequently reducing passive responses to aversive stimuli.

2.2 Experience of control increases positively motivated behaviors

In addition to promoting active avoidance responses to aversive stimuli and suppressing passive responses, perception of control also increases appetitive behavior, even in an aversive context (e.g., after a warning signal predicting an avoidable aversive outcome). In the example of the employees who find the weekly meeting unpleasant, an announcement that the meeting will commence in ten minutes is likely to affect the employees' behavior differently during those ten minutes. The employee who perceives little control over the aversive meeting may stay in place passively, whereas the employee who has learned to actively avoid the meetings might go to the break room for a snack.

Appetitive behavior when faced with a pending aversive, but controllable outcome is seen in versions of the signaled active avoidance paradigm where there is sufficient time between CS onset and the expected onset of the aversive US (Diehl et al., 2019). For example, if a relationship between a tone and painful shock has been established such that the shock

reliably occurs during the final 2 s of the 30 s tone, rodents show initial passive responses to the tone before the active avoidance response is learned, as reviewed earlier (Diehl et al., 2019; LeDoux et al., 2017). But an important additional observation is that, once the active response is well-learned, rodents will engage in appetitive behavior if it is available during the time after CS/warning signal onset but before the expected aversive outcome. That is, they will press a lever for a food reward even when a warning signal indicates a shock is forthcoming, and only engage the active avoidance response (move to the safe platform where the rewarding lever is unavailable) late in the time window (Bravo-Rivera et al., 2014;Bravo-Rivera et al., 2021; Diehl et al., 2019). This behavior appears partly reliant on a mechanism for inhibiting passive responses to the CS/warning signal as reviewed earlier, where the infralimbic cortex of mPFC detects controllability of the aversive outcome and signals amygdala to suppress passive responses that would preclude reward seeking during the delay (Diehl et al., 2019). Additionally, the prelimbic cortex of mPFC sends prominent projections to the ventral striatum that appear important in both active avoidance and reward seeking during the delay (Diehl et al., 2019; Sangha et al., 2020). The ventral striatum is critical not only in the active avoidance response but also in reward-seeking behavior (Cardinal, Parkinson, Hall, & Everitt, 2002; Knutson, Delgado, & Phillips, 2008; Tremblay, Worbe, & Hollerman, 2009). Although positively motivated behavior in this aversive but controllable context is not fully understood, one hypothesis is that the prelimbic cortex of mPFC is important for resolving motivational conflict between the reward-seeking vs active avoidance behaviors, allowing reward-seeking when a situation is deemed safe in the moment (Bravo-Rivera et al., 2021; Diehl et al., 2019). Alternatively, reward-seeking in this situation could be seen as a strategy to distract or upregulate positive affect to cope with the aversive context, but it should be noted that it only occurs once control over the aversive outcome is learned and passive responses are suppressed. In either alternative, the reward-seeking behavior in this situation is adaptive only as long as the individual eventually engages the active avoidance response. Importantly, there are individual differences in this behavior, with other individuals preferring to engage the avoidance response early in the window (foregoing the reward opportunity) or not at all (reward-seeking at the cost of shock), which may reflect the complexity of balancing rewards and aversive threats when responding in real situations (Bravo-Rivera et al., 2021). The prelimbic cortex, which is important for reward-seeking in this situation, is homologous to dorsal anterior cingulate cortex (dACC) in humans (Heilbronner et al., 2016). While the role of

human dACC in resolving conflict with competing goals is well-studied (Botvinick, Cohen, & Carter, 2004; Shenhav, Cohen, & Botvinick, 2016), there is limited research to help us understand how human appetitive behavior in aversive contexts is modulated by perceived control over aversive outcomes.

Research utilizing fMRI in humans suggests that typical neural responses to reward are altered in the context of aversive stressors. Ventral striatum anticipatory responses to monetary gain compared to no gain are reduced when expecting uncontrollable aversive shocks (Choi, Padmala, Spechler, & Pessoa, 2014). Following an acute stressor (cold pressor task; Schwabe & Schächinger, 2018), ventral striatum responses to the receipt of monetary gain vs loss are also reduced in ventral striatum (Porcelli, Lewis, & Delgado, 2012), but this effect may not be consistent with different types of stressors, and may differ between anticipatory responses vs responses to receipt of reward. For example, ventral striatum responses to monetary gain were not influenced in the context of aversive movie clips (Ossewaarde et al., 2011). Furthermore, an aversive context created by negative performance feedback increases anticipatory ventral striatum responses to monetary gain but decreases responses during receipt of monetary gain (Kumar et al., 2014). Other research shows that uncontrollable aversive (Pavlovian) cues (predicting an aversive taste) reduce instrumental approach behavior. This influence is related to an increase in correlation between vmPFC and striatum signals (Geurts, Huys, den Ouden, & Cools, 2013a). Furthermore, the influence is dependent on serotonin function (Geurts, Huys, den Ouden, & Cools, 2013b), and enhanced in depression (Nord, Lawson, Huys, Pilling, & Roiser, 2018). The mechanisms humans use to resolve conflict between uncontrollable aversive cues (promoting passive responses) and reward opportunities (promoting reward-seeking responses) are an active area of research (Guitart-Masip, Duzel, Dolan, & Dayan, 2014).

Despite important progress in understanding positively motivated behavior in aversive contexts, it is unclear how increasing the perception of control over aversive outcomes might influence reward-seeking responses. However, some research suggests that reward-seeking does increase when humans perceive control over aversive outcomes. For example, perceived control over aversive outcomes can increase persistence with a monetary reward-seeking goal in spite of aversive outcomes (Bhanji & Delgado, 2014), and can counteract acute stress-related decreases in persistence (Bhanji, Kim, & Delgado, 2016). Nonetheless, more research is needed to directly address positively motivated behavior in the context of controllable vs uncontrollable aversive outcomes.

3. Maintenance of avoidance responses and excessive avoidance

Avoidance behavior is sometimes framed as a maladaptive pattern of responding to stressors. Indeed, excessive avoidance behaviors are observed in obsessive compulsive disorder, social and generalized anxiety, post-traumatic stress disorder, and disorders of addiction (Baker, Piper, McCarthy, Majeskie, & Fiore, 2004; Bhanji, Delgado, & Ray, 2021; Fenster et al., 2018;Gillan et al., 2014; LeDoux et al., 2017; Urcelay & Prével, 2019). While this review has focused on situations where avoidance responses are unambiguously beneficial to the individual there are clearly many situations where avoidance responses may become excessive and maladaptive. For example, avoidance of anxiety triggers (e.g., social interaction) is effective to reduce anxiety, but avoidance becomes excessive in anxiety disorders and interferes with healthy behavior (LeDoux & Gorman, 2001; Shackman & Fox, 2016; White et al., 2017). Thus, in healthy functioning there must be a mechanism for limiting excessive avoidance behavior if the behavior is too costly or there is a change in the aversive outcome to be avoided (e.g., it becomes less aversive).

An interesting question is apparent in the signaled active avoidance paradigm that has been discussed here: how can the active avoidance behavior be influenced by the aversive outcome when the outcome no longer occurs once the behavior is well-learned (LeDoux et al., 2017)? In other words, if an individual makes the active avoidance response reliably when the warning signal is present, they will not experience the aversive outcome, and therefore cannot experience any changes in the aversive outcome. In the example of the employee who reliably avoids meetings, if the manager changed the meeting format to make the meetings more pleasant, the employee would not ever experience the change in pleasantness. In this case where an individual no longer experiences the aversive outcome, why does the avoidance behavior not extinguish similarly to other instrumental behaviors?

In fact, active avoidance responses have been shown to interfere with extinction of responses to the CS/warning signal in humans. In a paradigm where humans acquired a passive fear response to an aversive shock-predicting cue (skin conductance response increase), they then learned to actively avoid the shock by making a button press, and the passive fear response decreased. Then the cue was presented in extinction (i.e., without shock) and participants either had the avoidance button available to them or had it taken away. The presence of the avoidance response prevented

extinction of the passive fear response: participants continued to make the active avoidance response and continued to expect shock associated with the CS/warning signal (Lovibond, Mitchell, Minard, Brady, & Menzies, 2009). Furthermore, in a similar paradigm where the active avoidance response was made unavailable during extinction (by taking away the button), participants showed extinguished passive fear responses to the CS/warning signal presented without shock, as expected. When the avoidance response was reintroduced, however, participants resumed making the active avoidance response, despite having successfully completed extinction. Furthermore, if the avoidance response was made unavailable again, the passive fear response to the CS returned (Vervliet & Indekeu, 2015). These observations are consistent with the interpretation of avoidance responses as "safety behaviors" that inhibit extinction of passive fear responses (Urcelay & Prével, 2019; van Uijen, Leer, & Engelhard, 2018). The active avoidance response itself, however, is resistant to extinction, and returns easily when the response is available.

One perspective on the maintenance of active avoidance responses, even though aversive outcomes are not experienced in well-learned avoidance, is that the response becomes habitually controlled by the CS/warning signal rather than by the aversive outcome (Gillan et al., 2014; LeDoux et al., 2017; Urcelay & Prével, 2019). A habitual response can be identified as one that is insensitive to changes in outcome and is linked to a stimulus-sensitive (outcome-insensitive) neural circuit of lateral striatum (putamen), thalamus, and motor cortex (Ceceli & Tricomi, 2018). Research to understand neural underpinnings of habitual active avoidance response in humans is ongoing. However, it has been demonstrated that avoidance responses evoked by aversive Pavlovian cues (presented in extinction without aversive outcomes) are associated with increased fMRI BOLD in vmPFC and putamen (Lewis, Niznikiewicz, Delamater, & Delgado, 2013). Further research will help us better understand how avoidance responses may be maintained by a habitual system, and how these responses might be altered.

4. Conclusions

Whether an active avoidance response is adaptive or maladaptive depends on several factors, including the cost of the response, missed opportunities for learning changes in outcomes (e.g., an unpleasant meeting becoming pleasant), and situation specific demands. Active avoidance resembles an active coping strategy, in that it addresses the cause of a stressor

in order to alleviate it (Folkman & Lazarus, 1988; LeDoux & Gorman, 2001). Though active coping strategies are often considered adaptive, the constraints of a specific situation must be considered. For uncontrollable stressors, active coping strategies are ineffective compared to other strategies such as cognitive regulation, but when stressors are controllable active coping strategies are more effective (Troy, Shallcross, & Mauss, 2013). In this review we have discussed how individuals respond to stressors in active or passive ways via distinct pathways involving amygdala nuclei and ventral striatum, how controllability modulates those neural mechanisms via mPFC connections to amygdala and ventral striatum, and how active avoidance responses may be maintained potentially via habitual mechanisms involving lateral striatum.

The neural circuits that are identified in aversively motivated behavior form a foundation for further research to understand motivation in humans. For example, computational models have been developed to describe how the perception of control may influence neural pathways for passive and active responses to motivational stimuli (Dorfman & Gershman, 2019) and how striatum is involved in habit-based responses that are insensitive to changes in outcome value (Baladron & Hamker, 2020). These models can advance understanding of how these neural circuits function adaptively in some aversively motivated situations, and maladaptively in other situations as in the case of mental health disorders associated with excessive avoidance, including obsessive compulsive disorder, social and generalized anxiety, post-traumatic stress disorder, and disorders of addiction (Baker et al., 2004; Fenster et al., 2018; Gillan et al., 2014; LeDoux et al., 2017; Urcelay & Prével, 2019). The perception of control is an essential component of self-efficacy, which has broad effects on mental health and disorders of anxiety and addiction (Bandura, 1999; Bandura, Freeman, & Lightsey, 1999). Further understanding of the influence of perceived control on neural circuits of aversively motivated behavior can better identify mechanisms that are impaired or that may be utilized to improve mental health. The work reviewed here to understand neural mechanisms of aversively motivated behavior is a promising foundation for understanding the complexities of motivation.

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