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Review article

The study of active avoidance: A platform for discussion

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ABSTRACT

Traditional active avoidance tasks have advanced the field of aversive learning and memory for decades and are useful for studying simple avoidance responses in isolation; however, these tasks have limited clinical relevance because they do not model several key features of clinical avoidance. In contrast, platform-mediated avoidance (PMA) more closely resembles clinical avoidance because the response i) is associated with an unambiguous safe location, ii) is not associated with an artificial termination of the warning signal, and iii) is associated with a decision-based appetitive cost. Recent findings on the neuronal circuits of PMA have confirmed that amygdala-striatal circuits are essential for avoidance. In PMA, however, the prelimbic cortex facilitates the avoidance response early during the warning signal, perhaps through disinhibition of the striatum. Future studies on avoidance should account for additional factors such as sex differences and social interactions that will advance our understanding of maladaptive avoidance contributing to neuropsychiatric disorders.

1. Introduction

The study of fear and aversive learning is entering an exciting period. Three decades of research using Pavlovian fear (threat) conditioning have uncovered many of the neuronal circuit mechanisms necessary to associate a sensory stimulus (e.g. an auditory tone) with an aversive outcome (e.g. an electrical foot-shock), and to respond appropriately (for reviews, see Johansen et al., 2011; Herry and Johansen, 2014; Duvarci and Pare, 2014; Giustino and Maren, 2015; Do Monte et al., 2016). Auditory fear conditioning is elegant in its simplicity and enables cellular studies in animals and translation to humans. The most easily measured conditioned response in rodents is freezing: an automatic, species-specific defense response provided by evolution to counter potential threats (Blanchard and Blanchard, 1972; Fanselow, 1994). However, behavioral responses to learned threats can also be complex and decision-based, such as halting foraging for food or actively avoiding cues or places associated with danger. Avoidance of danger and its competition with foraging are common problems for rodents in the wild. In humans, avoidance can be a coping strategy to reduce the likelihood of harmful encounters (e.g. moving to the sidewalk to avoid a potential threat from an oncoming car that is honking at you). Avoidance becomes maladaptive, however, in neuropsychiatric disorders by interfering with other goal-directed activities (American Psychiatric Association, 2013). Therefore, the development of appropriate animal models could give rise to new approaches for the treatment of these disorders (Milad and Quirk, 2012; Rodriguez-Romaguera and Quirk, 2017; Diehl et al., 2018c; Singewald and Holmes, 2019).

Compared to conditioned freezing, it will be more challenging to uncover the neuronal mechanisms of decision-based avoidance responses. Because fear conditioning is thought to represent the first stage of avoidance learning (Mowrer and Lamoreaux, 1946), our increased understanding of fear circuits should accelerate active avoidance research. For example, the roles of specific subdivisions of the prefrontal cortex, amygdala, and striatum in fear learning have been extensively researched (Pezze and Feldon, 2004; Kravitz and Kreitzer, 2012; Giustino and Maren, 2015; Duvarci and Pare, 2014). Indeed, a lack of knowledge about fear conditioning and habit learning may have periled earlier attempts to uncover active avoidance mechanisms (Wendler et al., 2014; LeDoux et al., 2017). In recent years, a number of groups interested in aversive learning are shifting their focus away from simple classical fear conditioning (Servatius et al., 2008; Amir et al., 2015; Pare and Quirk, 2017; Fadok et al., 2017; Burgos-Robles et al., 2017; Kim and Jung, 2018; Kyriazi et al., 2018;Cain, 2019 Headley et al., 2019). The objective of this review, therefore, is to compare current active avoidance paradigms, their neural mechanisms, and relation to psychiatric disorders. Future research on avoidance will need to employ

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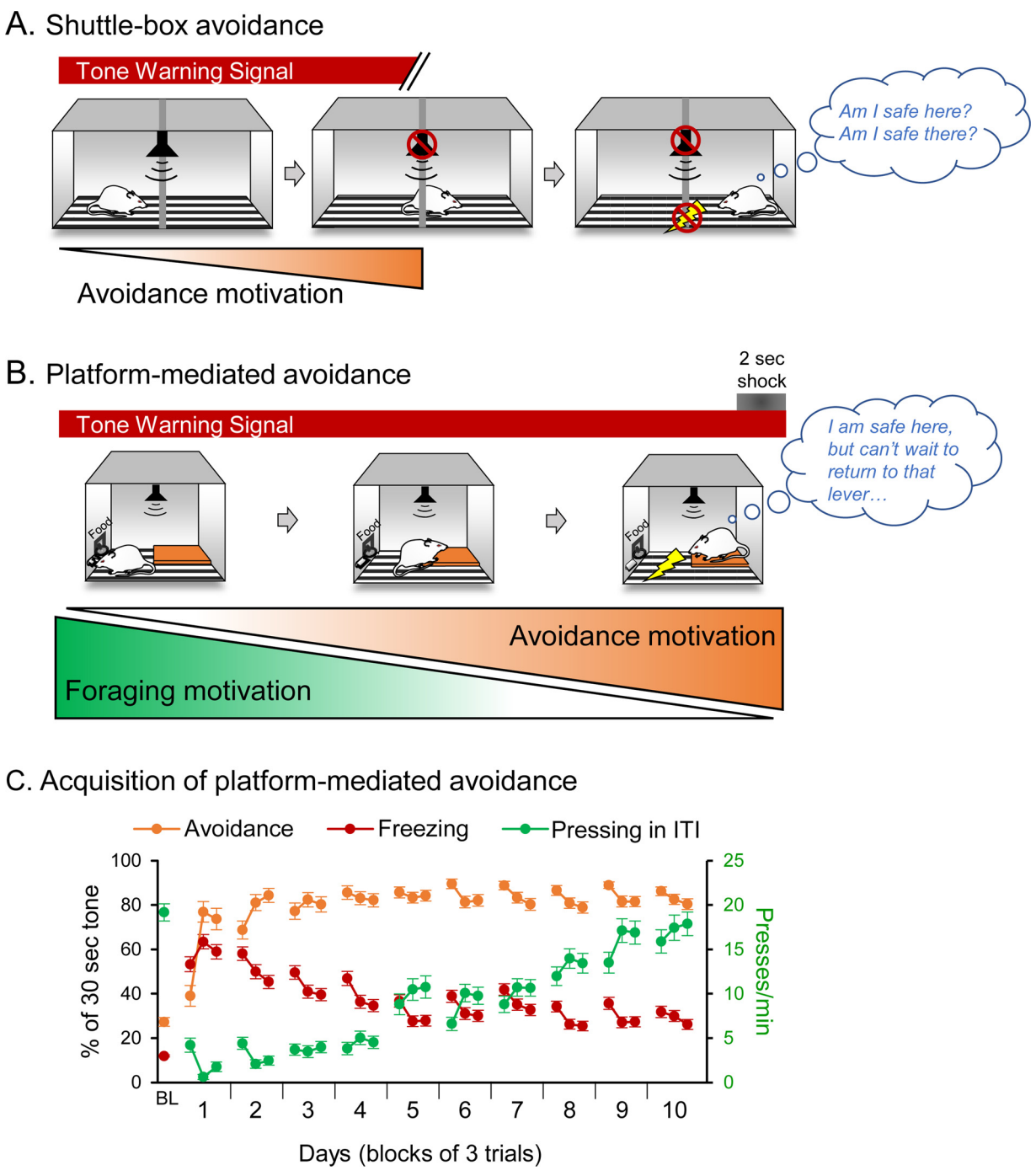

Fig. 1. Comparison of shuttle-box avoidance and platform-mediated avoidance tasks. **A**. Typical behavior of rats during the shuttle-box avoidance task. Following the onset of the tone warning signal, rats learn to avoid by moving to the opposite side of the box, which both terminates the tone and prevents the generation of a footshock. Because rats must enter a place where they were previously shocked, no place is associated with safety. **B.** Typical behavior of rats during the platform-mediated avoidance task (PMA). Following the onset of the tone warning signal, rats learn to stop pressing the bar for sucrose pellets and move toward the platform, so that they are no longer in contact with the grid floor. Performing this avoidance response does not terminate the tone or prevent the generation of a footshock; rats remain on the platform throughout the tone. In this way, rats are able to control their exposure to a shock, but not the presence of the shock or its predictive stimulus. While protecting them from shock, the platform also prevents rats' access to sucrose reward. **C.** Acquisition of PMA across 10 days of training. As training proceeds, avoidance (time spent on platform) increases (orange symbols), while freezing to the tone decreases (red symbols). The rate of bar pressing during the inter-trial interval (ITI) increases back to its pre-conditioning rate (green symbols). First data point shows the pre-conditioning baseline value (BL) to the first tone. All other data points are blocks of three tone trials. n = 82 rats. All data shown as mean ± SEM. Modified from Bravo-Rivera et al. (2014).

tasks that are more relevant to clinical syndromes in humans.

2. Traditional active avoidance tasks and their limitations

Several tasks have been used to study active avoidance. Unlike passive avoidance, in which an individual can avoid danger without requiring an overt behavioral response, active avoidance requires an overt behavioral response. Here, we focus on signaled active avoidance, in which a conditioned warning signal (WS) such as a tone predicts the occurrence of an aversive unconditioned stimulus (US), usually a

footshock (Mowrer, 1939; Kamin et al., 1963; Mowrer, 1960). The most commonly used active avoidance task is the two-way shuttle avoidance. Rodents learn shuttle avoidance in two stages (Mowrer and Lamoreaux, 1946; Levis, 1989). Initially, they learn the tone-shock association, evidenced by freezing to the tone. Next, animals run to the opposite chamber in response to the shock and quickly learn that they can terminate the WS and the shock by escaping into the adjacent chamber (Fig. 1A). After further training, animals learn that shuttling in response to the onset of the WS (before shock occurs) terminates the WS and prevents shock delivery. Across days of training, conditioned freezing to the WS diminishes as rats learn that the avoidance response reliably prevents the occurrence of shock (Kamin et al., 1963). In other tasks, animals are required to run on a wheel (Bolles et al., 1966; Gabriel et al., 1975) or press a lever (D'Amato and Schiff, 1964; Berger and Brush, 1975; Servatius et al., 2008) to terminate the tone and prevent the occurrence of shock.

While these paradigms have taught us much about active avoidance (Dinsmoor, 2001; LeDoux et al., 2017; Moscarello and Hartley, 2017; Cain, 2019), they are somewhat limited as models of naturally occurring avoidance. First, in none of these avoidance tasks (wheel-running, lever-pressing, and shuttle) is there a permanent safe place because rats both receive and avoid shock within the same location. For example, in the shuttle task, rats must enter a compartment in which it was shocked on a previous trial. Without a dedicated safe location, positional conflict can occur, leading to increased freezing. This can be a problem because conditioned freezing to the context (Bouton and Bolles, 1979; Kim and Fanselow, 1992) can interfere with expression of the instrumental response needed to avoid. This can cause rats to move very slowly, or even freeze. In fact, approximately one quarter of rats fail to express shuttle avoidance due to excessive freezing (Choi et al., 2010; Galatzer-Levy et al., 2014). Interestingly, freezing has the effect of masking avoidance because eliminating freezing by inactivating the central nucleus of the amygdala reveals the underlying avoidance behavior (Lazaro-Munoz et al., 2010). Thus, the circuits of the expression of conditioned freezing and conditioned avoidance appear to be separate.

A second limitation of these avoidance tasks is that there is no cost associated with performing the avoidance response. When danger is encountered in naturalistic settings, animals are usually seeking food, shelter, or mates (Kavaliers and Choleris, 2001). The interruption of these activities by avoidant behaviors constitutes a cost of avoidance. This phenomenon is clinically relevant because patients avoiding a perceived threat end up sacrificing activities that are otherwise rewarding or necessary for social functioning (Foa and Kozak, 1986). In the shuttle task, there is no cost to shuttle as this action does not require a sacrifice of any kind. A third limitation is that avoidance responses in these tasks often cause termination of the WS. The rat's ability to terminate both the WS and the shock demonstrates considerable control over the environment, but is this realistic? In natural settings, an individual's avoidance response does not eliminate the existence of a threat but decreases the likelihood of being harmed by that threat. For example, a rodent retreating to its burrow does not make the predator above disappear (it only obscures the view of the predator), in the same way that a person's decision to avoid traffic does not make an oncoming car disappear. Because our ability to alter the existence of external threats is limited, the avoidance-triggered termination of the WS (and even the US) in these tasks does not reflect the conditions of naturally-occurring avoidance. Some researchers have employed a constant CS duration in shuttle avoidance, which resolves this issue (Smith et al., 2002; Trigo et al., 2008; Carmona et al., 2014). Despite these limitations, shuttle avoidance and other traditional active avoidance tasks are useful for isolating avoidance circuits during no-cost conditions which do not compete with motivated behaviors.

3. Platform-mediated avoidance is well-suited for studying clinical avoidance

To study active avoidance in a more realistic manner, we made a simple modification of our auditory fear conditioning task, in which rats are exposed to tone-shock pairings while pressing a lever for sucrose pellets on a variable interval schedule of reinforcement (Estes and Skinner, 1941; Quirk et al., 2000). In platform-mediated avoidance (PMA), a 1 cm high platform is fixed in one corner of the behavioral chamber, located diagonally from the sucrose lever (Fig. 1B; for task details, see Bravo-Rivera et al., 2014). Similar to other active avoidance tasks, rats initially learn the tone-shock association and then discover that they can escape the shock (final 2 s of 30 s tone) by moving onto the platform. Next, rats learn that they can completely avoid the shock if they move onto the platform prior to the shock onset (on average, 5 s after tone onset). Early in training, the level of freezing to the tone is high and the rate of lever pressing during the inter-trial intervals (ITIs) is low (Fig. 1C). As rats progress through 10 days of training, freezing gradually decreases. Pressing during the tone remains low but pressing during the ITI gradually returns to pre-conditioning levels, reflecting rats' learning that the threat is limited to the tone period. Thus, avoidance behavior in PMA consists of halting food seeking and approaching a safety zone.

PMA is distinct from other avoidance tasks, such as lever press and shuttle avoidance, because the avoidance response does not terminate the WS. During PMA, the WS continues while the rat is waiting on the platform. Additionally, avoiding in PMA does not prevent the generation of a shock. By stepping onto the platform, rats have removed themselves from danger, in effect controlling their exposure to the shock rather than the existence of the shock or its predictive stimulus. This more closely resembles commonly encountered threats. Using the aforementioned example, the animal that hides in its burrow must wait to come out until the predator goes away. While it was originally proposed that the termination of the WS contributes to avoidance learning (Kamin et al., 1963; Keehn and Nakkash, 1959), our findings support the idea suggested by Bolles that this contribution is not essential (Bolles et al., 1966). However, in the absence of WS termination, how does the rat in PMA know it needs to continue executing the avoidance during the tone? On some trials, rats fail to avoid the shock. In addition, some rats on the platform show "testing" behavior by placing their front paws onto the bars to confirm the presence of shock during the WS. This occurs on occasional trials toward the end of the 10 days of training and may be important for maintaining the avoidance response by reinforcing that the tone still predicts danger and also that the platform is a safe zone.

PMA bears some resemblance to early avoidance tasks in which rats were required to jump up to a safe platform. Rats could jump 25 cm up onto a shelf to avoid a shock (Maatsch, 1959) or jump 7.5 cm up onto to a shelf to avoid excessive heat (Henderson and Graham, 1979). In addition to requiring a jump, differences between these tasks and PMA include the absence of a predictive WS and the absence of a foraging cost. The cost of PMA mirrors clinical avoidance, which competes with goal-directed behaviors (Foa and Kozak, 1986; Breslau, 2001; Asmundson et al., 2004). The motivation to press a lever for reward also serves to decrease freezing. Freezing is further reduced in PMA because rats do not enter an area in which they were previously shocked. Thus, the relatively low levels of freezing observed in PMA (~60% on day 1 to ~30% on day 10, see Fig. 1C) do not prevent rats from moving to the platform. Consequently, unlike the shuttle task, almost all rats learn and express PMA (> 95%).

PMA is not without its own limitations. Because it involves reward/avoidance conflict, PMA requires food/water restriction to generate reward seeking motivation. Recent studies have shown that food restriction can alter neuronal circuits of motivation (Nieh et al., 2015; Huang et al., 2016; Verma et al., 2016). Therefore, if a researcher wishes to study active avoidance under homeostatic conditions, then

PMA may not be the optimal task. Moreover, although a strength of PMA is that freezing does not compete with avoidance, freezing-induced blockade of avoidance in the shuttle task could model non-adaptive responses to trauma often observed in PTSD.

In summary, shuttle avoidance may be more appropriate for studying basic principles of active avoidance that can be directly compared with decades of prior research, whereas PMA more closely resembles real life avoidance by adding a decision-based cost contingency. During PMA: 1) avoidance competes with foraging behavior, 2) avoidance does not artificially terminate the WS or the US, 3) rats are not required to move toward (or remain in) a place where they were previously shocked. Moreover, once learned, the levels of freezing do not compete with expression of PMA, disambiguating the effects of experimental manipulations on the circuitry of avoidance vs. the circuitry of conditioned fear.

4. Neural circuitry of active avoidance: amygdala, striatum, and prefrontal cortex

The amygdala is essential for acquiring the tone-shock association (LeDoux, 2000; Maren and Quirk, 2004; Maren, 2005; Ponnusamy et al., 2007; Johansen et al., 2011; Lüthi and Lüscher, 2014; Sears et al., 2014; Do Monte et al., 2016). Consequently, the amygdala is essential for both the learning and initial expression of active avoidance. Both pre-training (Lazaro-Munoz et al., 2010) and post-training (Choi et al., 2010) lesions of the basolateral amygdala (BLA) impaired shuttle avoidance, and pharmacological inactivation of BLA impaired expression of PMA (Bravo-Rivera et al., 2014; see Fig. 2A). Increased activity in the amygdala has been correlated with expression of active avoidance, as demonstrated with the activity marker cFos in the shuttle task (Martinez et al., 2013), lever press task (Jiao et al., 2015), and PMA (Bravo-Rivera et al., 2015; Martínez-Rivera et al., 2018), as well as with unit recording in the wheel-running task (Poremba and Gabriel, 1999; Maren et al., 1991). Dopamine signaling in the ventral striatum (VS) is required for shuttle avoidance (Darvas et al., 2011) and notably, a crossed-inactivation study has implicated amygdala projections to VS in shuttle avoidance (Ramirez et al., 2015). The VS is thought to inhibit the substantia nigra pars reticulata in order to execute the avoidance response (Hormigo et al., 2016).

Apparent differences in neuronal circuitry between the shuttle task and PMA arise, however, in the recruitment of the prefrontal cortex. In shuttle avoidance, inactivation of the infralimbic cortex (IL), but not the prelimbic cortex (PL), impaired shuttle avoidance (Moscarello and LeDoux, 2013). In PMA, inactivation of these structures had opposite effects: impairment with PL inactivation, but no impairment with IL in activation (Bravo-Rivera et al., 2014). The discrepancy with IL could be due to the differing effects of freezing behavior in the two tasks. IL inactivation increased freezing in both tasks (Moscarello and LeDoux, 2013; Bravo-Rivera et al., 2014), but only in the shuttle task did this interfere with expression of avoidance; rats in PMA were still able to step onto the platform. Thus, while IL may be essential for reducing freezing in avoidance, it is not essential for avoidance itself. What is less clear is why PL is necessary for PMA but not shuttle avoidance. One possibility is the difference in timing of lesions in the two studies (pre-training in shuttle and post-training in PMA). Another possibility is the presence of conflict between avoidance and foraging in PMA, which has been proposed to recruit PL during motivational conflict (Illescas-Huerta et al., 2019) as well as cost-benefit decision-making (Friedman et al., 2015). We have recently suggested that PL may be more modulatory than essential. Inactivating PL impaired the expression of PMA early in the tone (when avoidance is less urgent), but not late in the tone (when avoidance is more urgent; Fig. 2A) (Diehl et al., 2018a). In contrast, inactivation of BLA impaired avoidance throughout the tone (Fig. 2A; Bravo-Rivera et al., 2014).

More clues about the role of PL in active avoidance are suggested by unit recording and optogenetic findings (Diehl et al., 2018a). Following PMA training, PL neurons exhibited robust inhibitory responses to the tone. Opposing these inhibitory responses with optogenetic stimulation delayed the expression of avoidance or blocked it entirely (Diehl et al., 2018a). Inhibitory responses in PL were observed in rats trained in PMA, but not those trained in auditory fear conditioning, suggesting that avoidance was signaled by PL inhibition. Interestingly, inhibitory responses in PL were observed whether or not the rat avoided on a given trial, suggesting that PL inhibition signals the avoidability of the shock, perhaps acting as a "discriminative stimulus" (Cain, 2019) that lets the rat know it has the option to avoid. Given the robust projection from PL to VS (Sesack et al., 1989; Ding et al., 2001; Vertes, 2004; Gabbott et al., 2005) including those onto inhibitory interneurons (Berke, 2011), we suggest that PL inhibitory responses to the WS serve to disinhibit the driving of VS output neurons by basal amygdala (BA) inputs, hence promoting avoidance (Fig. 2B). Excitatory responses in PL were correlated with platform entry (Diehl et al., 2018a), which is consistent with cFos studies showing that increased PL activity correlates with avoidance behavior (Martinez et al., 2013; Bravo-Rivera et al., 2015). These excitatory responses are likely transmitted to BA rather than to VS, as indicated by a recent retrograde labeling study (Martínez-Rivera et al., 2018).

In summary, it appears that PL is important for avoiding early during the tone, when the rat must weigh avoidance against foraging to decide if (and when) it will initiate platform approach. PL promotes avoidance during this period through inhibitory responses that disinhibit VS responses to BA inputs. PL also promotes avoidance by exciting BA neurons that may, in turn, excite VS outputs. As the tone progresses and shock becomes imminent, BA excitation of VS increases so that disinhibition by PL is no longer necessary (Fig. 2B). Thus, while BA inputs to VS are necessary throughout the tone, PL inputs to VS are only necessary early in the tone, when decisions are made regarding a more ambiguous threat. Experiments employing optogenetics are currently underway to test this circuit (Diehl et al., 2018b).

5. Modeling maladaptive avoidance with PMA

Excessive avoidance can be maladaptive due to missed opportunities for reward (Lovibond and Shanks, 2002; Vervliet and Indekeu, 2015), and missed opportunities for extinction of trauma-associated cues (Foa and Kozak, 1986). Excessive avoidance can occur when the individual is unable to learn that a previous threat is no longer dangerous (extinction deficits), or is unable to recall this learning (Bravo-Rivera et al., 2015; Vervliet and Indekeu, 2015). Excessive avoidance is a hallmark of anxiety disorders such as PTSD and OCD (Breslau, 2001; Asmundson et al., 2004; McGuire et al., 2012), but is also observed in phobias (Eaton et al., 2018), depression (Trew, 2011) and autism (Madipakkam et al., 2017). In contrast to excessive fear, the neuronal mechanisms of excessive avoidance are not well-understood, and animal models such as PMA may lead researchers toward improved treatments for patients suffering from neuropsychiatric disorders (Bravo-Rivera et al., 2015; Rodriguez-Romaguera and Quirk, 2017; Diehl et al., 2018c; Cain, 2019).

Persistent avoidance related to extinction deficits has been studied in the PMA task using the activity marker cFos (Bravo-Rivera et al., 2015). Rats failing to extinguish avoidance after two days of extinction training had excessive activity in BLA, VS, and PL, consistent with the proposed circuit of avoidance expression shown in Fig. 2B. Rats showing persistent avoidance also exhibited reduced activity in IL, consistent with impaired extinction of the tone-shock association. Unlike extinction of fear, extinction of active avoidance involves two components: extinction of the tone-shock association and extinction of the avoidance behavior. To distinguish between these two, Bravo-Rivera et al., 2015 also assessed extinction of avoidance with the platform removed, so that the tone-shock association could be extinguished in the absence of the option to avoid. After rats extinguished their conditioned fear responses (measured by suppression of food

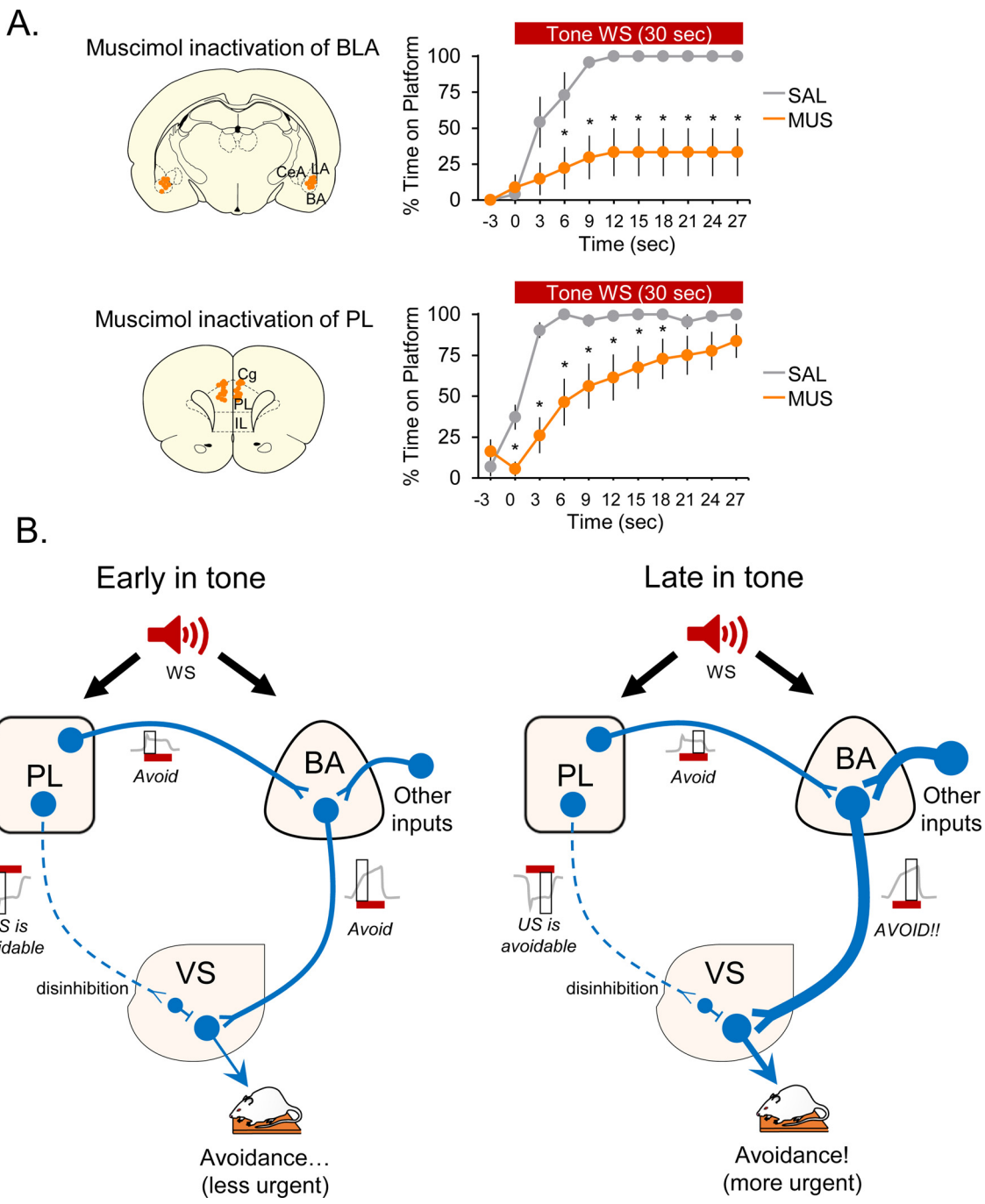

Fig. 2. Proposed circuitry of platform-mediated avoidance at different timepoints during the tone. **A.** *(Left)* Coronal schematics of BLA (top) and PL (bottom) inactivationwith muscimol (MUS) or saline (SAL), showing location of cannula tips. *(Right)* Time spent on the platform (in 3 s bins) during the tone revealed that BLA inactivation blocked avoidance in MUS rats (top) across the entire tone compared to SAL controls (rptd. meas. ANOVA, post hoc Tukey). Data from Bravo-Rivera et al. (2014). PL inactivation significantly impaired avoidance early, but not late, in the tone (bottom), in MUS rats compared to SAL controls (rptd. meas. ANOVA, post hoc Tukey). Modified from Diehl et al., 2018a. **B.** *(Left)* Early during the tone, inhibitory responses are observed in PL neurons (dashed axon), which likely project to inhibitory interneurons in the VS. Inhibitory responses in PL would promote avoidance by disinhibiting the response of VS output neurons to BA inputs. PL neurons also show excitatory responses prior to platform mounting, which could project to BA neurons and facilitate avoidance. *(Right)* Late in the tone, as avoidance becomes more urgent, PL disinhibition of VS is maintained and BA excitation of VS increases in response to other inputs (thick axon), thereby over-riding any inhibitory effects of PL inputs. Thus, expression of urgent avoidance (when shock is imminent) occurs independently of PL. Grey trace is hypothetical neural activity with black box indicating activity during the early or late periods of the tone (red bar). All data shown as mean ± SEM. *p < 0.05. Abbreviations: BA – basal amygdala; BLA – basolateral amygdala; CeA – central nucleus of the amygdala; IL – infralimbic cortex; LA – lateral amygdala; PL – prelimbic cortex; VS – ventral striatum.

seeking), the platform was returned in a subsequent test session. Rats showing persistent avoidance under these conditions had excessive activity only in PL and VS; BLA and IL showed a normal fear extinction profile. Thus, PL-VS connections appear to support maladaptive avoidance independently of tone-shock association circuits. Furthermore, unlike extinction of conditioned fear, PL plays a key role in the extinction of PMA, as BDNFergic inputs from the ventral hippocampus to PL are both necessary for, and activated by, extinction training (Rosas-Vidal et al., 2018).

In order to understand maladaptive avoidance with regard to OCD,

the PMA task has been modified to study extinction-based treatment of avoidance-related compulsions in OCD, known as exposure-with-response-prevention (ERP; Rachman et al., 1971; Foa et al., 2005; Simpson et al., 2008; Franklin and Foa, 2011). In ERP therapy, patients are exposed to triggers for their compulsions but are prevented from expressing their compulsions, in order to extinguish the compulsive behavior. Similar to PTSD, ERP is only effective for a subset of patients (Foa et al., 2005; Simpson et al., 2008; Foa et al., 2013). ERP was modelled in the PMA task by preventing rats' access to the platform during extinction (extinction-with-response-prevention, or Ext-RP; Rodriguez-Romaguera et al., 2016). After several days of Ext-RP training, when the platform was again accessible, approximately 25% of rats showed persistent avoidance. Persistent avoidance could be eliminated by either pharmacologically inactivating the orbitofrontal cortex or applying deep brain stimulation (DBS) to the VS, a rodent homologue of effective sites of DBS for the treatment of OCD in humans (Rodriguez-Romaguera et al., 2016). In agreement with human studies of OCD (Evans et al., 2004; Menzies et al., 2008; Milad and Rauch, 2012), persistent avoidance in PMA is associated with hyperactive orbitofrontal areas.

A poor clinical response to exposure-based therapies in OCD may reflect the repetitive nature of compulsions in this disorder. It has been suggested that OCD patients are prone to exhibit habit learning that drives the repetition of avoidance behaviors that are no longer necessary (Gillan et al., 2015). Consistent with this, extending PMA conditioning from 8 days to 20 days impairs Ext-RP, and augments the percentage of rats showing persistent avoidance (Martinez-Rivera et al., 2018). cFos immunohistochemistry revealed marked differences in patterns of avoidance-related neuronal activity in trained vs overtrained groups, suggesting possible mechanisms by which individuals fail ERP therapy. Thus, the circuits of goal-directed avoidance may differ from the circuits of the more habitual avoidance associated with OCD.

6. Active avoidance in humans

Human studies examining active avoidance are emerging, often comparing avoidance training with extinction of fear. There is a long-standing idea that conditioned avoidance is resistant to extinction (Solomon and Wynne, 1954; Rescorla, 2003; Lovibond et al., 2009). In support of this, it was shown that avoidance behaviors with little cost can persist following Pavlovian extinction (Vervliet and Indekeu, 2015), similar to rodents (Bravo-Rivera et al., 2015; Rodriguez-Romaguera et al., 2016). Avoidance training can even impair subsequent extinction training (Rattel et al., 2017). Indeed, high levels of avoidance can prevent extinction from occurring ("protection from extinction" effect) which can account for the high prevalence of avoidance symptoms in anxiety disorders. However, a recent study comparing subjects with avoidance training to subjects with extinction training (as a "yoked" control group) found that avoidance produced longer-lasting reductions in fear that continued through re-conditioning (Boeke et al., 2017), supporting the idea that learning "controllability" may be clinically beneficial (Maier, 2015).

Neuroimaging studies of human active avoidance parallel rodent studies. Avoidance activates both the amygdala and the ventral striatum, and their activities are correlated (Delgado et al., 2009; Levita et al., 2012), consistent with BA activation of VS in rodents. The vmPFC, which is the human homologue of rodent IL (Bicks et al., 2015; Heilbronner et al., 2016) is also activated during avoidance (Boeke et al., 2017; Wendt et al., 2017), consistent with IL reduction of conditioned fear responses (Moscarello and LeDoux, 2013; Bravo-Rivera et al., 2014). Avoidance-related activity of the dorsal anterior cingulate (dACC), a human homologue of rodent PL (Bicks et al., 2015; Heilbronner et al., 2016), was correlated with activity in both striatum and amygdala, consistent with prefrontal modulation of the amygdala-striatal circuit. It is interesting to note that avoidance symptoms in PTSD correlate with resting state activity of dACC (Marin et al., 2016). To better model clinical avoidance, future studies of human avoidance should include an appetitive cost of avoidance which could recruit dACC (Collins et al., 2014).

7. Future directions for active avoidance

Future tasks including a cost of avoidance will need to consider the magnitude of the cost vs. the magnitude of the competing reward. Increasing the cost of avoidance can reduce the decision to avoid (Rattel et al., 2017) or facilitate the pursuit of conflicting reward (Friedman et al., 2015). The cost of avoidance can increase when it interferes with a time-limited access to reward. In the PMA task, foraging/avoidance competition is minimal because sucrose is also available during the ITI when the tone is off. Restricting sucrose access to the period of the tone maximizes this conflict and reveals different "strategies" for conflict resolution. Preliminary data from our group show that rats exhibit one of three strategies under these conditions: 1) they remain on the platform throughout the tone, 2) they remain at the sucrose lever throughout the tone, or 3) they divide their time, spending the early part of the tone at the lever and the later part of the tone at the platform, the latter of which is the most prevalent phenotype (Bravo-Rivera et al., 2016). These three subgroups can be useful for understanding maladaptive behaviors as well as revealing distinct patterns of activation within avoidance and reward circuits (Burgos-Robles et al., 2017).

Future avoidance studies will need to assess sex differences, given that females show more avoidance compared to males following a traumatic event (Kessler et al., 1995). Prior studies have found that males acquire active avoidance more quickly than females (Gray and Lalljee, 1974; Farr et al., 1995; Beck et al., 2011; Yokota et al., 2017; but see ; Denti and Epstein, 1972; Rubio et al., 1999). In contrast, females extinguish the avoidance response more quickly than males but only when training is combined with a safety-associated cue in rodents (Beck et al., 2011; Radell et al., 2015) and in humans (Sheynin et al., 2014). This may be at odds with clinical findings showing that females have an increased risk of developing an anxiety disorder (Bangasser et al., 2018; Altemus et al., 2014). Therefore, future studies should address the extent to which the addition of safety cues during extinction training would reduce avoidance symptoms in males vs. females.

Thus far, the study of active avoidance has been investigated in the absence of any social factors. How might the presence of social cues alter the learning or expression of avoidance? Only one animal study has addressed social factors in active avoidance. Augmenting social interactions with pair-housing facilitated the learning of extinction of avoidance (Smith et al., 2016). Other behavioral paradigms have examined social factors in fear learning (Olsson and Phelps, 2007; Debiec and Olsson, 2017), decision making (Tremblay et al., 2017), and addiction (Heilig et al., 2016). For example, addicted rats will abstain from taking drugs in order to interact with another rat (Venniro et al., 2018). Such studies demonstrate the impact social interactions have on behavior. It would be interesting to examine whether positive or negative types of social interactions facilitate or impair the acquisition of avoidance, respectively. From a clinical perspective, understanding how social interactions impact maladaptive avoidance could lead to beneficial treatments, given that positive social support systems have been shown to alleviate symptoms of anxiety (Boscarino, 1995; Brewin et al., 2000; Platt et al., 2014), PTSD (Arnberg et al., 2012), and depression (McGuire et al., 2018).

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