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ORIGINAL INVESTIGATION

Avoid-approach conflict behaviors differentially affected by anxiolytics: implications for a computational model of risky decision-making

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Abstract
Whether fear or anxiety is expressed is thought to depend on an animal's proximity to threat. In general, fear is elicited when threat is proximal, while anxiety is a response to threat that is distal and uncertain. This threat gradient model suggests that fear and anxiety involve non-overlapping neural circuitry, yet few behavioral paradigms exist that elicit both states. We studied avoid-approach conflict in rats that were behaving in a predator-inhabited foraging arena task that involved tangible threat and reward incentives. In the task, rats exhibited a variety of both fearful and anxious behaviors corresponding to proximal and distal threat, respectively. We then administered ethanol or diazepam to the rats in order to study how anxiolytics affected these fear and anxiety behaviors. We discovered that both ethanol and diazepam attenuated proximal-threat fear-like behaviors. Furthermore, we found that diazepam, but not ethanol, increased distal-threat anxiety-like behavior but also made rats less risk-averse. Finally, we describe how decisional conflict can be modeled as a partially observable Markov decision process and characterize a potential relationship between anxious behavior, diazepam's ability to suppress hippocampal theta oscillations, and hippocampal representations of the future.

Keywords Decision-making · Anxiety · Fear · Diazepam · Ethanol · Anxiolytics · Avoid-approach conflict · Foraging theory · Prospection · Computational modeling

Introduction

Fear and anxiety are distinct states (Dias et al. 2013; Perusini and Fanselow 2015), with fear being a set of defensive responses to visible and immediate danger (e.g., fighting, fleeing, or freezing) while anxiety is a form of risk-assessment involving the anticipation of potential future threat. Evidence supports the idea that behavioral responses to threat vary depending on the perceived proximity to the threat source, with anxiety-like behaviors (e.g., hesitation and avoidance) being elicited when threat is distal and fear-like behaviors being elicited when threat is proximal (Mobbs and Kim 2015).

Threat processing frameworks have developed around this notion of a threat gradient. For example, Fanselow and Lester's "threat imminence continuum" characterizes the progression through four states of threat processing that depend on the visibility and proximity of threat: (i) The preferred phase during which there is no threat, (ii) the pre-encounter phase during which the prey is vulnerable to threat (e.g., foraging) but no threat is detected, (iii) the post-encounter phase during which a threatening agent is detected but does not pursue the prey, and (iv) the circa-strike phase during which the threat source actively pursues the prey (Fanselow and Lester 1988). Fanselow and Lester's model was then elaborated on in Mobbs' "Survival Optimization System" wherein there are five strategic systems that align with the four stages of the threat imminence continuum: (i) Prediction strategies, (ii) prevention strategies, (iii) threat orienting strategies, (iv) threat assessment strategies, and (v) defensive strategies

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(Mobbs et al. 2015). Prediction and prevention occur during both the preferred and pre-encounter states, threat orienting and threat assessment occur during post-encounter states, and defensive reactions occur during circa-strike states.

These frameworks harken back to early cognitive theories of anxiety which postulated that anxiety arises from negative evaluations of episodic future construction generated by hippocampal-cortical, hippocampal-accumbens, and hippocampal-amygdala interactions (Gray and McNaughton 1982; Beck et al. 1985/2005). These anxiety frameworks differ from models of fear wherein most instantiations of fear are thought to result from either Pavlovian associations or species-specific, genetically inherited circuitry (Bolles 1970; LeDoux 2012). Together, these frameworks and anatomical demarcations suggest that fear and anxiety should be both behaviorally and pharmacologically dissociable. However, few tasks clearly elicit and behaviorally dissociate fear and anxiety, making it difficult to study both states simultaneously. Naturalistic choice conflict paradigms in which reward incentives (e.g., hunger) are pursued at the risk of incurring punishment (e.g., exposure to a threatening predator) have been used since as early as the 1940s, and these avoid-approach conflict tasks are often structured so as to elicit both fear and anxiety (Miller 1944). In recent years, these ethological approaches have largely been neglected in favor of more controlled Pavlovian fear conditioning paradigms (see reviews: Mobbs and Kim 2015; Pare and Quirk 2017).

One recently developed avoid-approach conflict paradigm is the predator-inhabited foraging arena (Choi and Kim 2010; Amir et al. 2015; Kim et al. 2015, 2018). In this task, food-deprived rats are trained to forage for food pellets on a linear track with an enclosed nest-space at one end. A robotic predator is then introduced at the opposite end of the linear track from the enclosed nest-space, and the predator probabilistically surges forward and attacks when the rat approaches the feeder site near the robot. Following predatory attack, rats typically flee back to the enclosed nest-space (Choi and Kim 2010) and proceed to exhibit various fear- and anxiety-like avoid-approach conflict behaviors.

The key difference between anxiety and fear on the predator-inhabited foraging arena can be operationalized by the reaction of the rat to the proximity of the predator—distal, approaching, and proximal—both pre- and post-attack. Post-attack, rats retreat and spend time hesitating at the opening of the enclosed nest-space (Amir et al. 2015) before deciding either to turn back into the nest-space or venture out and risk obtaining a food pellet. This conflict-associated hesitation is reminiscent of another risk-assessment behavior: the stretch-attend posture seen at the entry into novel, open spaces (Grewal et al. 1997) or into spaces laced with predator scent (Blanchard et al. 2001). Furthermore, Amir et al. reported that rats in the predator-inhabited foraging arena would occasionally leave the nest-space and begin their approach toward the "dangerous" feeder site adjacent to the predator, and then, in what appeared to be a change-of-mind event, would turn around and retreat back into the nest-space, thus aborting the foraging attempt and failing to obtain the food pellet at the predator-occupied feeder site (Amir et al. 2015). Interestingly, data show that rats are more likely to decide to leave the nest and forage for food if they have had amygdala lesions or intra-amygdalar infusions of muscimol (Choi and Kim 2010). Furthermore, it has been shown that there are two subsets of basolateral amygdala neurons that ramp in activity at the nest-space choice-point: one population prior to retreating back into the nest (pause-retreat) and the other before deciding to initiate a foraging attempt (pause-approach) (Amir et al. 2015).

One challenge with rodent decision-making tasks is finding a balance between ethological validity and task complexity (Juavinett et al. 2018). The predator-inhabited foraging arena is a model of real-world foraging involving deliberation, approach incentives, and a sustained and tangible threat source that strikes a balance of low task complexity and high ethological validity, a valuable ratio for studying the interaction between fear, anxiety, and decision-making under naturalistic conditions. In contrast to many fear and anxiety assays, a benefit of this paradigm is that it is effectively one-dimensional. This allows for a clear-cut and continuous quantification of binary economic "stay-or-go" decision-making along the full length of the track while providing access to similar circuitry and behavior involved in more complex, two-dimensional, real-world foraging scenarios. Furthermore, it has the advantage of evoking a variety of fear- and anxiety-like hesitation behaviors that neatly map onto the threat gradient continuum.

Although the design of the predator-inhabited foraging arena, with its spatially distinct distal-to-proximal threat gradient, allows for the differentiation of fear- and anxiety-like behaviors, no one has yet looked at what effect anxiolytics have on these behaviors. Verifying that anxiolytics do in fact reduce the anxiety-like behaviors seen on the predator-inhabited foraging arena would support the task's construct validity and serve as an important data point if it is to be used more widely in the study of fear and anxiety in rodents. Furthermore, it is known that there are sex differences in how males and females of various species (e.g., mice, rats, non-human primates, and humans) express fear and anxiety both neurophysiologically and behaviorally (Johnston and File 1991; Crepeau and Newman 1991; Maeng and Milad 2015; Yokota et al. 2017), yet all experiments on the predator-inhabited foraging arena to date have used only male rats (Choi and Kim 2010; Amir et al. 2015; Kim et al. 2015, 2018).

To explore these two questions, we acutely administered ethanol and diazepam, two pharmacological agents that have well-characterized anxiolytic effects (Wilson et al. 2004), to both male and female rats in the predator-inhabited foraging arena. We found that both ethanol and diazepam reduced approach time toward the threat source, indicating an attenuated fear response to proximal threat. This is consistent with the effect of ethanol and diazepam on other threat paradigms

(Blanchard et al. 1990a, b, 1993). Ethanol, however, had no effect on deliberative pausing behavior at the nest-space choice-point (an anxiety-like behavior) while diazepam increased the amount of deliberative pausing at the nest-space choice-point. Lastly, diazepam, but not ethanol, increased the probability of the rats making risky foraging decisions following choice-point deliberation.

Materials and methods

Subjects

Both male ($n = 8$) and female ($n = 6$) Brown Norway rats aged 8–10 months were used as subjects. All rats were maintained on a 12:12 hr light/dark cycle. Rats were food-restricted such that they had 1 hr per day to work for food in the foraging arena. Rats were always kept above 80% free-feeding weight and had unlimited access to water outside of the foraging arena. All procedures were approved by the University of Minnesota (UMN) Internal Animal Care and Use Committee (IACUC) and were performed in accordance with NIH guidelines.

Surgery

Following 7 days of linear track training, rats were chronically implanted with a light-emitting diode (LED) fixed to the skull surface with metabond. Rodents were anesthetized throughout the duration of the surgery (0.5–2% isoflurane mixed with medical-grade O_2 via nosecone). To ensure rapid recovery, rats were given pre-surgery antibiotics (penicillin G, 120 kunits/kg) and post-surgery Baytril at 25 mg/kg for 3 days post-surgery. Rats were recovered from surgery in an incubator to maintain body temperature and they received Children's Tylenol post-surgery to alleviate discomfort. Rats were given 72 hrs to recover before resuming behavioral training.

Task and data collection

The foraging arena was 1.16 m long and 33 cm wide with walls 60 cm tall. An overhead video camera tracked animal position from the head LED at 30 fps.

Behavioral procedure

There were three phases of the predator-inhabited foraging arena: linear track training, injection habituation, and attack sessions (see Fig. 1). During all three phases of the task, sessions lasted 1 hr and rats began each session in the nest-space.

Phase 1: During the linear track phase, rats learned to shuttle back-and-forth on a linear track to receive food pellets at either end. Food pellets were only delivered at one of the feeders once the other feeder had been visited; thus, rats needed to alternate between feeders to continually receive food. One end of the linear track had a partially enclosed "nest-space", a high-walled room continuous with the linear track via an open doorway referred to as the "choice-point". After ~ 10 days of linear track training, the rats transitioned to phase 2 of the task.

Phase 2: During the injection habituation phase, rats received saline injections intraperitoneally (i.p.) prior to linear track training. Following 2 days of i.p. habituation, rats proceeded to phase 3 of the task.

Phase 3: During the attack phase, rats received either drug or vehicle i.p. injections 5 min prior to being placed in the predator-inhabited foraging arena. Prior to the beginning of each session, a wall by the feeder site opposite the nest-space was removed, and a robotic predator (SPIK3R, LEGO® MINDSTORMS® EV3) was placed in the open space near the feeder site. For the first 15 laps, the robot remained stationary. After the first 15 laps, the robotic predator would surge forward and attack the foraging rat with a 20% probability (i.e., on any given lap there was a 1/5 chance of the robot attacking) as it approached the feeder site adjacent to the predator.

Pharmacological manipulation

Diazepam (2 mg/kg; Sigma) was dissolved in Tween 20 to prepare a stock solution, which was then diluted with 0.9% saline. The vehicle (10% Tween 20 in saline) was used as a control solution. Ethanol (1 g/kg) was prepared from 95% ethanol (Decon Labs) diluted with saline for a final concentration of 30% *v*/*v* to keep injection volumes below 5 mL/kg. Saline was used as a corresponding control solution. We chose these doses for both diazepam and ethanol due to their approximately matched anxiolytic efficacy (Wilson et al. 2004). All injections were administered i.p. 5 min prior to each session.

Data analysis

All data were processed in MATLAB (MathWorks, Natick, MA) and statistically analyzed using JMP Pro 14 (SAS, Cary, NC). All figures depict the mean ± s.e.m. Statistical significance was assessed using an alpha value of 0.05. Matched pairs or two-sample Student's *t* tests were used as indicated in each figure.

Results

We trained food-deprived rats to forage in a linear track arena in which they had to leave an enclosed nest-space to receive food located at the opposite end of the track. Importantly, both the zone 1 and zone 3 food ports would only reset once the rat had visited the opposite feeder site. Once rats were sufficiently

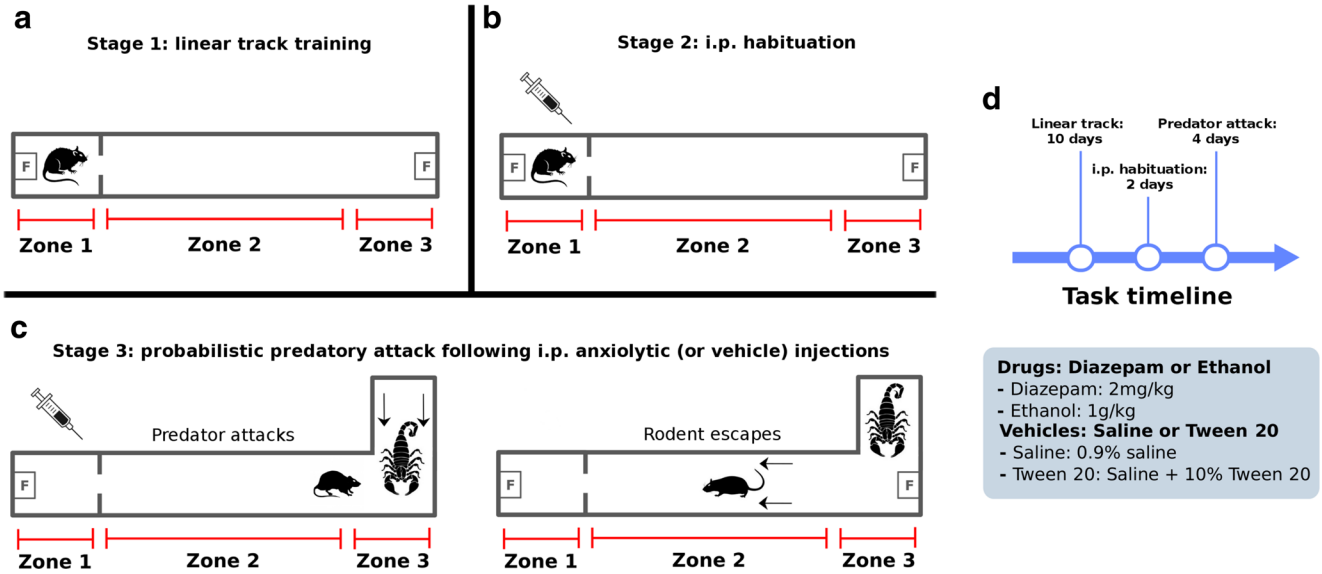

Fig. 1 Task design. **a** In the linear track training stage, food-deprived rats learned to move from Z1 → Z3 → Z1 etc. to receive food at food ports denoted "F". **b** Same as in **a** with the exception that the rat received saline i.p. injections 5 min prior to the session starting. **c** A robotic predator was introduced into the arena and the rat received drug (diazepam or ethanol) or vehicle (saline or Tween 20) i.p. injections 5 min prior to the session starting. Now, when the rat crossed from Z2 → Z3 there was a 20% chance of the predator surging forward and attacking the rat. During these attack epochs, rats typically froze and retreated back to the nest-space (Z1) without retrieving the food in Z3. **d** A timeline depicting the course of the experiment for each subject and the four drug conditions that were counterbalanced across the four attack days for each subject

trained such that they were able to stay above 80% free-feeding weight from daily 1 hr sessions on the linear track, we habituated them to i.p. injections for 2 days then we introduced a robotic predator (SPIK3R, LEGO® MINDSTORMS® EV3) to the arena situated near the feeder site opposite the nest-space. When the rat transitioned from zone 2 to zone 3, the robot would surge forward and attack the rat with a 20% probability (Fig. 1). During these attacks, the robotic scorpion charged forward toward the foraging rat and repeatedly snapped its pincers while emitting clicking sounds. Following predatory attack, rats typically fled to the nest and proceeded to exhibit a variety of fear- and anxiety-like hesitation behaviors for the duration of the session. For example, rats exhibited slower zone 1 ("safe") to zone 3 ("dangerous") approach times (i.e., slow "outbound" laps, Fig. 2), more zone 2 "change-of-mind" events (Fig. 3), more hesitation at the nest-space choice-point (Fig. 4), and heightened risk-aversion (Fig. 5). Slower "safe-to-dangerous" outbound laps and an increase in the number of change-of-mind events occurred as threat became more proximal. The predator became fully visible to the rats when they were roughly midway down the linear track, which would coincide with the location where mid-track abort "change-of-mind" events were observed. Thus, in keeping with the threat gradient model, we classified these "visible-and-proximal" threat-induced behaviors as being fear-like. Conversely, both choice-point hesitation and subsequent retreat decisions during risky decision-making occurred on this task when threat was distal; thus, we categorized these two behaviors as being anxiety-like. In order to test the effects of anxiolytics on these fear and anxiety behaviors, we administered either ethanol or diazepam 5 min prior to an attack session. We interleaved anxiolytic injections with their vehicle controls. Drug administration was counterbalanced across all subjects using the following four permutations: Tween 20, diazepam, saline, ethanol; saline, ethanol, Tween 20, diazepam; diazepam, Tween 20, ethanol, saline; and ethanol, saline, diazepam, Tween 20.

Both diazepam and ethanol reduced the duration of approach to danger

To determine if rats distinguished between dangerous (i.e., "outbound" laps when rats transitioned from zone 1 to zone 3 [Z1 → Z3]) and safe directions (i.e., "inbound" laps when the rats transitioned from Z3 → Z1) on the task, we quantified the time it took rats to run risky outbound laps (i.e., potential predatory attack) versus safe inbound laps (i.e., no risk of predatory attack) during attack sessions. Inbound laps were significantly faster than outbound laps (Fig. 2b; matched pairs t test, $t(13) = 4.72$, $p = 0.0002$), and risky outbound laps were faster under ethanol (Fig. 2c; matched pairs t test, $t(13) = 3.24$, $p = 0.0032$) and diazepam (Fig. 2d; matched pairs t test, $t(13) = 2.80$, $p = 0.0075$) relative to their vehicle controls. We found no significant differences in lap duration between males and females (Fig. 2e; two-sample t test, $t(12) = 1.29$, $p = 0.2193$).

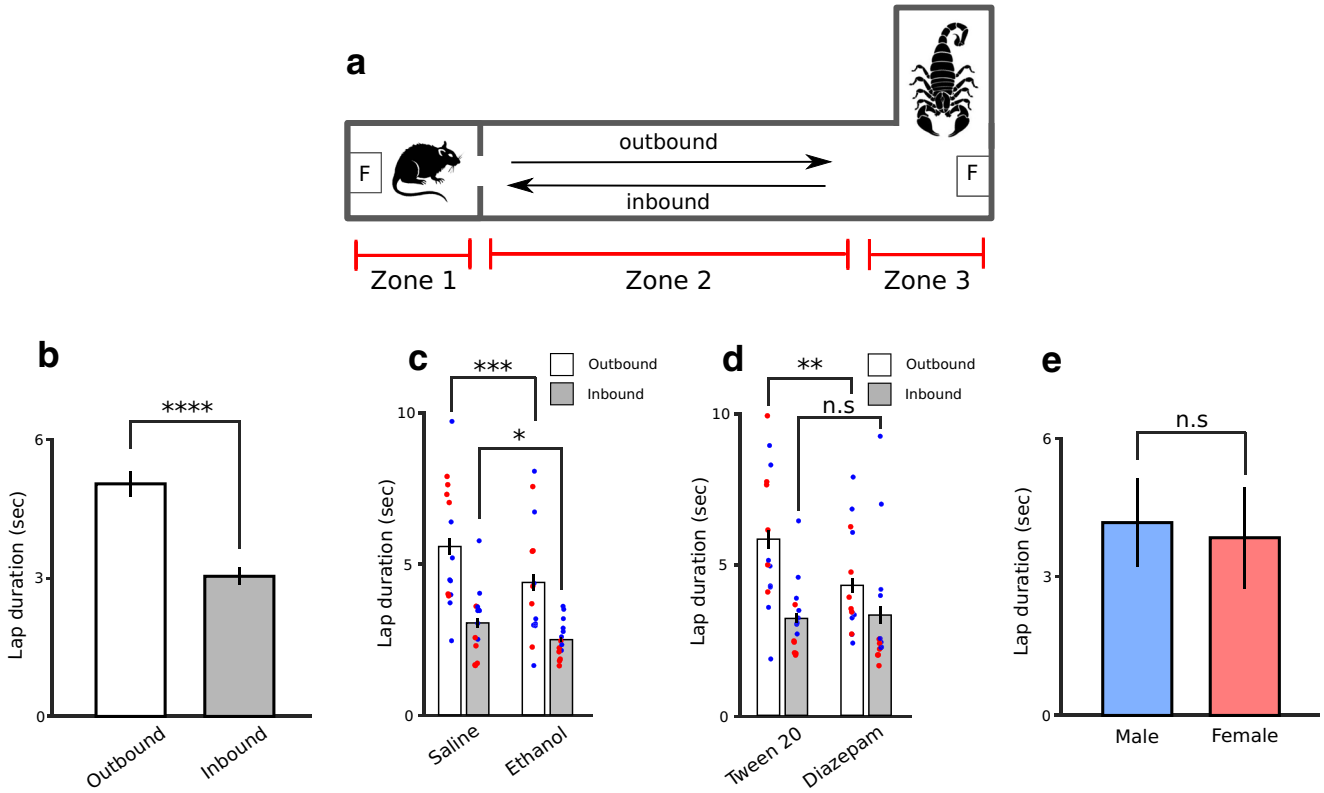

Fig. 2 Inbound versus outbound lap duration. **a** Schematic demonstrating the directionality of an inbound versus an outbound lap. **b** Safe inbound laps were faster than risky outbound laps (matched pairs *t* test, $t(13) = 4.72$, $^{****}p = 0.0002$). **c** Risky outbound laps were faster under ethanol than its vehicle control saline (matched pairs *t* test, $t(13) = 3.24$, $^{***}p = 0.0032$). Safe inbound laps were also found to be slightly faster under ethanol when compared to saline (matched pairs *t* test, $t(13) = 2.60$, $^{*}p = 0.0218$). **d** Risky outbound laps were faster under diazepam than its vehicle control Tween 20 (matched pairs *t* test, $t(13) = 2.80$, $^{**}p = 0.0075$), but no significant difference was found for inbound laps. **e** There was not a significant difference in lap duration (outbound and inbound laps pooled) between males and females (two-sample *t* test, $t(12) = 1.29$, $p = 0.2193$). Blue circles = males, red circles = females. Data are mean ± s.e.m. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.005$, $^{****}p < 0.001$

Both diazepam and ethanol reduced the number of change-of-mind events

As previously reported, we observed that rats that had recently experienced predatory attack would leave the nest-space, slowly approach the dangerous food source, pause, and then turn around and return back to the nest-space (i.e., Z1 → Z2 → Z1), thus giving up the opportunity to receive food (Amir et al. 2015). We quantified the number of these mid-track abort (MTA) "change-of-mind" events as well as a control behavior, anti-MTA's (i.e., Z3 → Z2 →Z3). MTAs were far more likely to occur than their control behavior, anti-MTAs (Fig. 3b; matched pairs *t* test, $t(13) = 3.24$, $p = 0.0032$). Interestingly, both ethanol (Fig. 3c; matched pairs *t* test, $t(13) = 2.12$, $p = 0.0268$) and diazepam (Fig. 3d; matched pairs *t* test, $t(13) = 2.17$, $p = 0.0245$) reduced the number of MTA events when compared against their vehicle controls. There was not a significant difference in MTA count between males and females (Fig. 3e; two-sample *t* test, $t(12) = 0.57$, $p = 0.5792$).

Diazepam, but not ethanol, increased the amount of time spent hesitating at the choice-point

As noted in the introduction, hesitation at the exit of the enclosed nest-space is an anxiety-like behavior reminiscent of stretch-attend posture and open-space entry hesitation seen in a variety of anxiogenic tasks. Consistent with previous work (Amir et al. 2015), we found that rats would pause in the nest-space doorway before deciding to either approach the food source in zone 3 or retreat back into the nest. We defined the deliberative pausing zone (DPZ) around the transition point from zone 1 to zone 2 and quantified epochs in which the rat entered the DPZ (the "pause zone" in Fig. 4a) and stayed there for > 2 s and < 5 min. Interestingly, while we found no difference in deliberative pausing between saline and ethanol (Fig. 4b; matched pairs *t* test, $t(13) = 1.58$, $p = 0.0689$), rats spent more time pausing at the choice-point with diazepam than with Tween 20 (Fig. 4c; matched pairs *t* test, $t(13) = 2.19$, $p = 0.0234$). There was no significant difference in

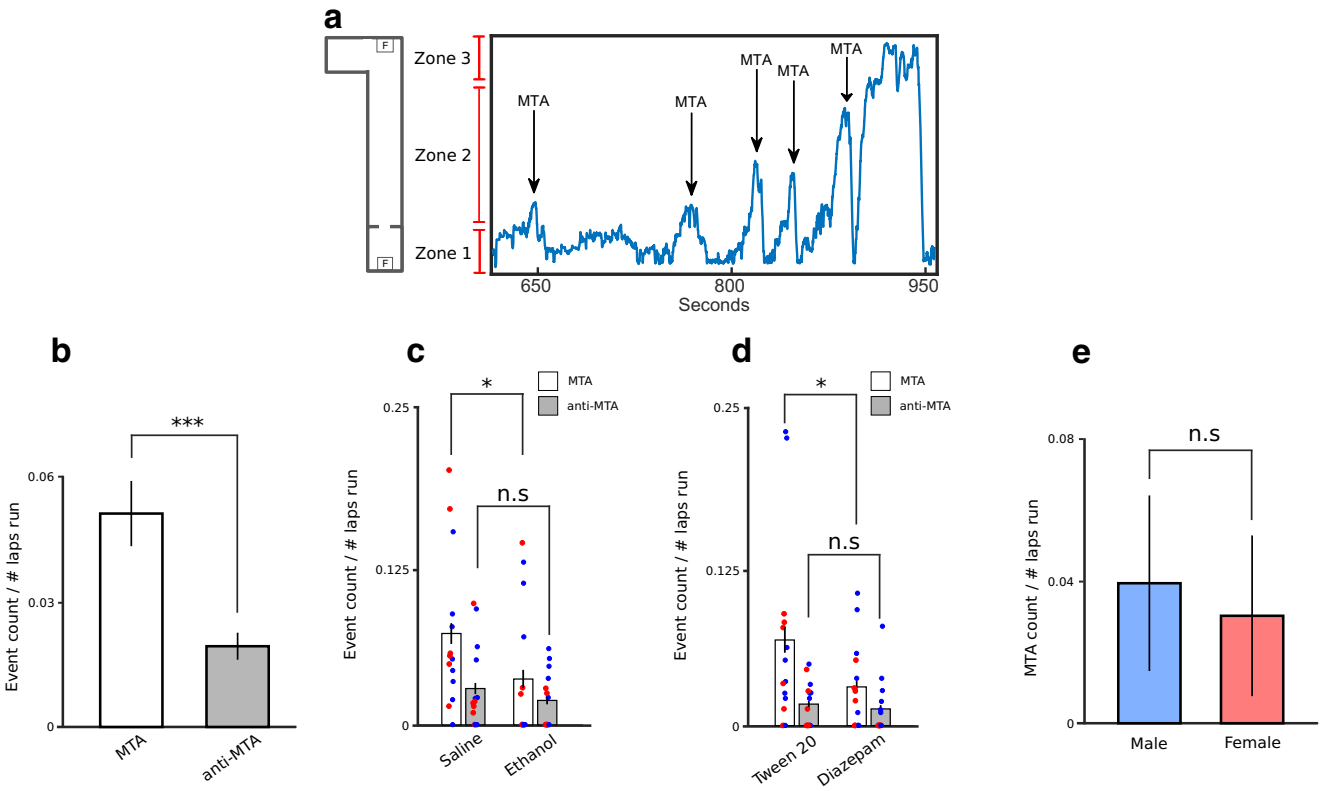

Fig. 3 Mid-track "change-of-mind" events. **a** A representative trace of five consecutive mid-track aborts (MTAs) from one animal in the span of 300 s. MTAs were operationalized as the rat leaving Z1, entering Z2, then returning back to Z1 without having entered Z3 to receive food (i.e., Z1 → Z2 → Z1). The anti-MTA control behavior measured when the rat left Z3, entered Z2, and returned to Z3 without having entered Z1 to receive food (i.e., Z3 → Z2 → Z3). **b** MTAs were more likely to occur than their control behavior, anti-MTAs (matched pairs *t* test, $t(13) = 3.24$, $^{***}p = 0.0032$). **c** Ethanol reduced the number of MTA events when compared against saline (matched pairs *t* test, $t(13) = 2.12$, $^{*}p = 0.0268$). **d** Diazepam reduced the number of MTA events when compared against Tween 20 (matched pairs *t* test, $t(13) = 2.17$, $^{*}p = 0.0245$). **e** There was not a significant difference in MTA count between males and females (two-sample *t* test, $t(12) = 0.57$, $p = 0.5792$)

deliberative pausing between males and females (Fig. 4d; two-sample *t* test, $t(12) = 0.93$, $p = 0.3676$).

Diazepam, but not ethanol, increased the number of risky outbound journeys following choice-point hesitation

Following deliberative pausing at the choice-point, the rat must decide to either retreat back into the nest or to leave the nest and journey out to zone 3 to get food. In order to explore how anxiolytics affected the rats' risk profiles, we quantified the number of these pause-then-approach (risk-taking) versus pause-then-retreat (risk-averse) events. After entering the nest doorway choice-point and pausing, rats were overall more likely to retreat than to approach (Fig. 5b; matched pairs *t* test, $t(13) = 4.46$, $p = 0.0006$). Intriguingly, while there was no difference between ethanol and saline in the tendency to retreat or approach (Fig. 5c; matched pairs *t* test, $t(13) = 0.88$, $p = 0.8022$), rats were more likely to approach and less likely to retreat under diazepam as opposed to its vehicle control (Fig. 5d; matched pairs *t* test, $t(13) = 2.65$, $p = 0.0100$). We also found that males were more likely than females to retreat following deliberation at the choice-point (Fig. 5e; two-sample *t* test, $t(12) = 3.46$, $p = 0.0047$).

Discussion

We found that rats were slower on risky outbound journeys than on safe inbound journeys (Fig. 2), performed more MTAs on outbound rather than inbound journeys (Fig. 3), and retreated more often than they approached after pausing at the nest-space choice-point (Fig. 5). With both ethanol and diazepam, we found a decrease in the duration of risky outbound journeys (Fig. 2) and a reduction in the number of MTA events (Fig. 3). However, diazepam, but not ethanol, increased the amount of time rats spent pausing at the choice-point (Fig. 4) and increased the number of pause-then-approach events while decreasing the number of pause-then-retreat events (Fig. 5). We found no sex differences across any of the behaviors of interest except avoid-approach

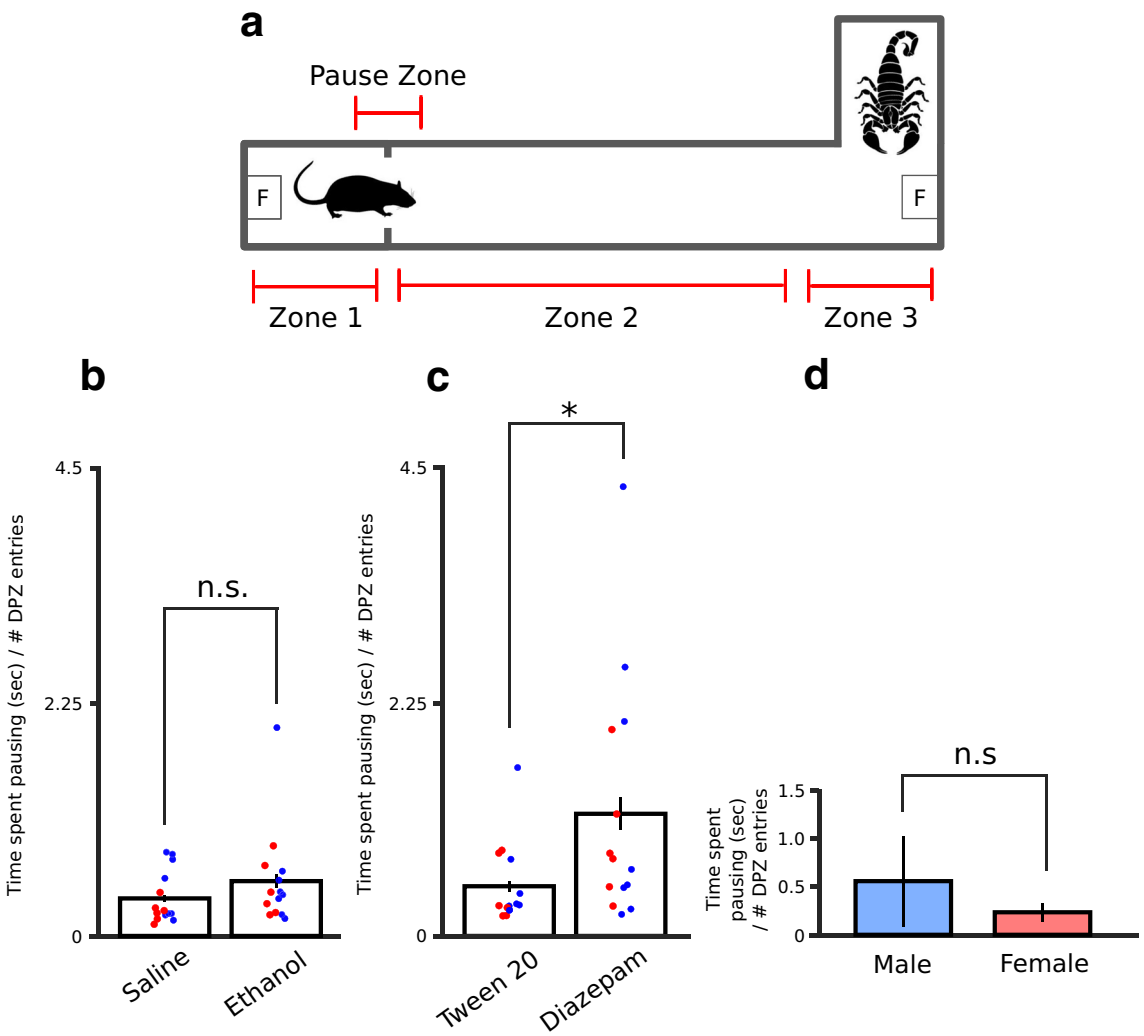

Fig. 4 Hesitation at the choice-point. **a** Schematic of a rat pausing at the nest-space choice-point before either deciding to leave the nest and risk foraging for food or retreat back into the nest. **b** There was no significant difference in deliberative pausing between ethanol and saline (matched pairs *t* test, $t(13) = 1.58$, $p = 0.0689$). **c** Rats spent more time pausing at the choice-point under diazepam than under Tween 20 (matched pairs *t* test, $t(13) = 2.19$, $^*p = 0.0234$). **d** There was not a significant difference in deliberative pausing between males and females (two-sample *t* test, $t(12) = 0.94$, $p = 0.3676$)

decisions following hesitation at the choice-point. However, it is possible that our sample size may be underpowered to reliably detect sex differences. Altogether, we found that two acutely administered anxiolytics, ethanol and diazepam, had different effects on decision-making behavior in a naturalistic avoid-approach conflict task. These data suggest that while both ethanol and diazepam dampened proximal-threat fear responses (Figs. 2 and 3), only diazepam increased distal-threat choice-point deliberation and, interestingly, this increased deliberation time resulted in more, not fewer, risky decisions to approach the threat source.

Our findings reveal that the anxiety-like behaviors seen in the predator-inhabited foraging arena are significantly diminished by anxiolytics, thus lending validity to the notion that this task can be used to model anxiety. The experiment presented here used single doses of ethanol and diazepam consistent with the dose range reported in similar behavioral pharmacology studies (Blanchard et al. 1990a; Blanchard et al. 1993; Treit et al. 1993). While there is an extensive literature describing the anxiety-related dose-response properties of both ethanol and diazepam (Blanchard et al. 1990b; Grewal et al. 1997; Kang-Park et al. 2004; Jiménez-Velázquez et al. 2010), it would be valuable for future work to investigate how the fear- and anxiety-like behaviors quantified on this task change with various doses of these two drugs in order to characterize the full dose-dependent response profile as has been done with other anxiogenic tasks (Blanchard et al. 1993; Wilson et al. 2004).

Interestingly, our data are at odds with some of the results reported in other anxiogenic tasks. For example, ethanol has been shown to increase formerly anxiogenic exploratory

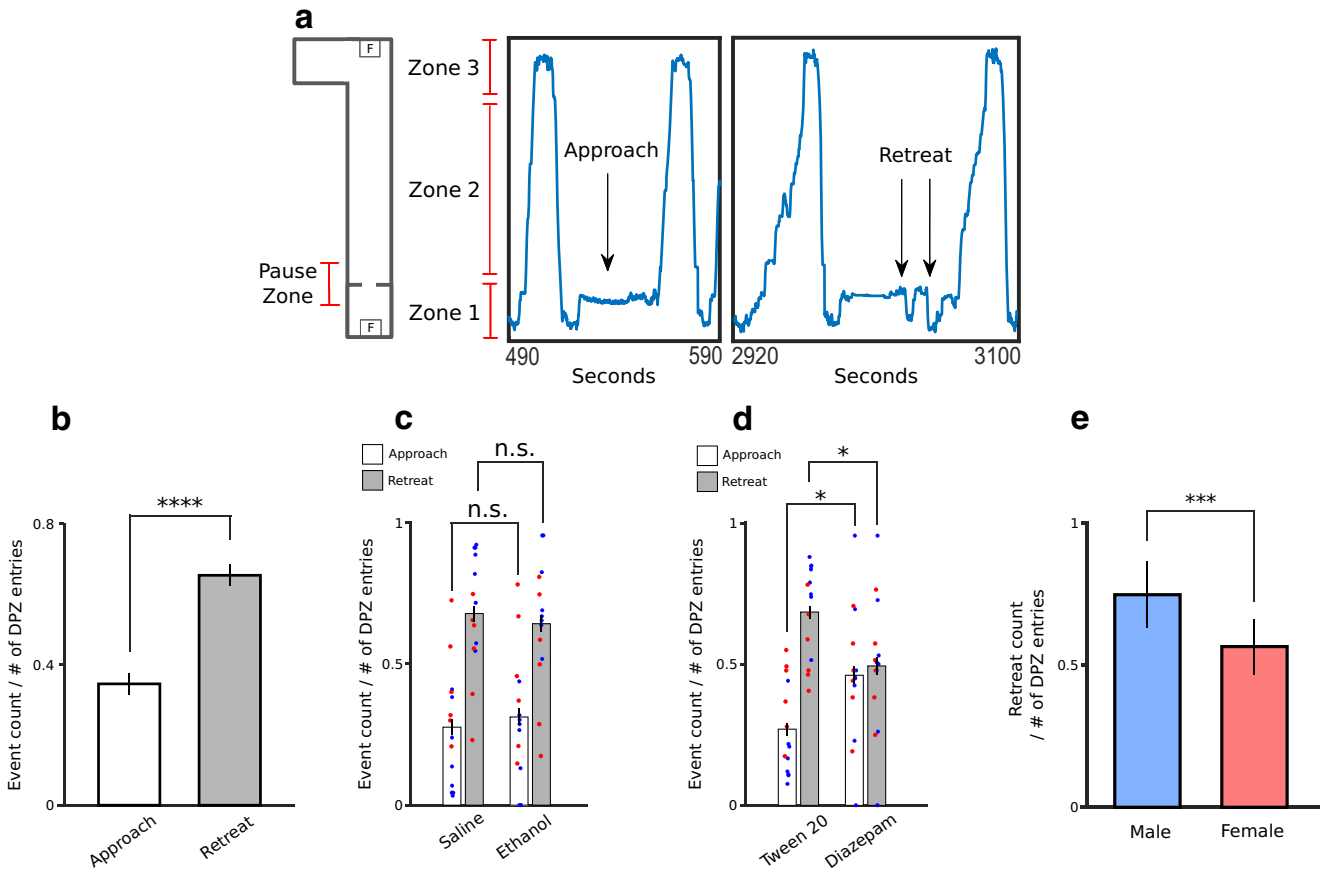

Fig. 5 Pause-then-approach versus pause-then-retreat behavior. **a** A representative trace of a pause-approach event (middle panel) and a pause-retreat event (right panel) obtained from one animal in the same session but at different time points in that session. **b** After entering the nest doorway choice-point and pausing, rats were more likely to retreat than to approach (matched pairs *t* test, $t(13) = 4.46$, $^{****}p = 0.0006$). **c** There was no difference between ethanol and saline in the tendency to retreat or approach (matched pairs *t* test, $t(13) = 0.88$, $p = 0.8022$). **d** Rats were more likely to approach and less likely to retreat under diazepam when compared to vehicle control (matched pairs *t* test, $t(13) = 2.65$, $^{*}p = 0.0100$). **e** Males are more likely than females to retreat following deliberation at the choice-point (two-sample *t* test, $t(12) = 3.46$, $^{***}p = 0.0047$)

behavior in the open field arena and elevated plus maze (Prunell et al. 1994; Ferreira et al. 2000; Wscieklica et al. 2016) whereas ethanol did not increase rats' willingness to engage in risky foraging in our data (Fig. 4b). This is likely due to the different cognitive demands made by the two anxiogenic task types and highlights the fact that non-overlapping neural circuits may be engaged during such traditional anxiety assays (e.g., elevated plus maze and the open field arena) as opposed to avoid-approach conflict resulting from foraging in the face of a visible and active threat source (e.g., the predator-inhabited foraging arena).

It has been theorized that distal threat induces anxiety-like behaviors (e.g., hesitation), while proximal threat induces fear-like behaviors (e.g., freezing, fighting, fleeing) (Fanselow 1994; Mobbs et al. 2015). Interpreted under this threat gradient model, both ethanol and diazepam appeared to attenuate the fear response induced by proximal threat in our task (i.e., faster approach times and reduction of MTAs) while diazepam, but not ethanol, increased risk-assessment behavior seen when the threat was distal (i.e., increased choice-point hesitation). Current theories differentiate between multiple decision-making systems (i.e., action-selection systems), each of which is mediated by non-overlapping neural circuits. In the context of threat processing, these theories postulate separate and dedicated decision-making algorithms for defensive reflexes, fear conditioning, innately aversive stimuli or contexts, and conflict (LeDoux and Daw 2018). Our data suggest that ethanol and diazepam affect different components of these decision-making circuits.

A Markov model of risky decision-making

We posit that episodic future thinking and non-local cost-benefit analysis are neural algorithms central to certain forms of anxiety. Specifically, we posit that deliberative forms of anxiety such as those seen during motivational conflict require a mental simulation of future scenarios, a representation of state-outcome contingencies, and a

valuation of those expected outcomes in order for conflict to be resolved and an action to be selected. Furthermore, we argue that this process can be modeled as a partially observable Markov decision process wherein the agent iterates through a loop of belief-state updating until a state inference is made, a decision threshold is passed, and an action is selected.

A Markov model is a mathematical description characterizing the behavior of a system that probabilistically transitions through a series of states over time. There are four major types of Markov models: Markov chains, hidden Markov models, Markov decision processes, and partially observable Markov decision processes. A Markov chain (MC) describes a system in which there are a number of discrete observable states (S) with probabilistic transitions between those states (e.g., $S_1 \rightarrow S_1 = 0.2$ while $S_1 \rightarrow S_2 = 0.8$). A hidden Markov model (HMM) is related to a Markov chain with the exception that the states themselves are unobservable, but the outcome of being in a given state is observable. As such, the present state can only be inferred from the observable outcomes and a probabilistic model of the parameters governing the unobservable states. Crucially, MCs and HMMs both involve systems lacking agency. A Markov decision process (MDP) accounts for a decision maker's ability to act and, in so doing, induce a state transition. Thus, in an MDP, each action (A) available to the agent has an associated set of observable states with associated state transition probabilities (e.g., $S_1, A_1 \rightarrow S_1 = 0.1$, $S_1, A_1 \rightarrow S_2 = 0.9$). Furthermore, in each state, there can be an associated reward (R) or punishment (P) value. Lastly, a partially observable Markov decision process (POMDP) is like an HMM that accounts for a decision maker capable of taking actions, inducing state transitions, and receiving rewards and punishments. The agent in a POMDP attempts to infer the state it is in by not only having a functional model of the parameters governing the unobservable states and their transitions, but also by means of exploratory actions that yield observations (O) which provide sensory evidence for the state the agent is currently occupying.

We propose that the motivational conflict underlying risky (i.e., costly and multivariate) decision-making can be modeled as a POMDP in which the agent performs exploratory behavior in the form of mental simulations (i.e., (Simulated State|Simulated Action) = (SS|SA)) to obtain observations of what is likely to happen in those simulated states (i.e., Expected(Outcomes|Simulated State) = E(O|SS)) (Fig. 6). Crucially, the values associated with these observations (i.e., V(O|SS)) are used to update the agent's belief about the state it is currently occupying, and this belief-state update informs action selection (i.e., V(SA|E(O)) (Fig. 6). The agent is attempting to maximize R (e.g., access to food and safety) while minimizing P (e.g., exposure to danger and threat), thus

$$A(S_c) = \arg\max_v [V(O_n|SS_n)]$$

where $A(S_c)$ is the action taken in conflict state S_c, V is value (a weighted sum of R and P), O_n is the nth simulated outcome, $\arg\max_v$ is the maximal $V(O_n)$ for the nth iteration through the POMDP, and SS_n is the nth simulated state. When $A(S_c)$ exceeds some decision threshold (e.g., to either approach or avoid), the agent then selects that corresponding action (e.g., in the predator-inhabited foraging arena, either approach the food source, hesitate, or retreat back into the nest). Two possible models of how this can be achieved are a continuous integration to threshold (Fig. 6, lower left) or a series of non-additive, discrete simulation space samples until one generated value passes a decision threshold (Fig. 6, lower right). Importantly, the baseline at which the value signal begins can be modeled as an incentive parameter that can start closer to or farther away from one of the decision thresholds depending on the internal state of the agent (e.g., if the rat is hungry, the baseline starts closer to the approach threshold, Th_{App}). According to our POMDP algorithm, the belief-state updating loop repeats until a given cycle through the POMDP succeeds in generating a value signal V(SA|E(O)) that passes some confidence threshold for making a state inference I(S|V(SS)), thus resulting in a decision threshold being passed and an action being selected (Fig. 6).

In contrast to risky decision-making scenarios wherein the agent might have time to deliberate between options, there are also instances of explicit and immediate threat that require rapid action to ensure survival. This general "detect-and-evade" algorithm can be modeled as a simple Markov decision process. In such situations, the agent transitions from a safe state (S_S) to a state of threat detection (S_T). The agent, upon detecting threat, mobilizes (e.g., changes in heart rate, attentional allocation, and circulating glucocorticoid levels) and executes an action (a) in the set of hard-wired, species-specific defense behaviors (A, such that a∈A). This threat-evasion loop repeats until the agent either returns to a safe state or is captured and killed by the threat (Fig. 7).

Mapping avoid-approach conflict behavior to neuronal circuit computations

The threat-gradient framework posits that distal threat promotes anxiety-like behaviors (e.g., choice-point hesitation on the predator-inhabited foraging arena) while proximal threat promotes fear-like behaviors (e.g., mid-track aborts and slow approach to threat on the predator-inhabited foraging arena). Here, we argue that the underlying circuitry governing these two behavioral classes are not only computationally but neurophysiologically dissociable.

It is becoming increasingly clear that the hippocampus plays a central role in decision-making during avoid-approach conflict scenarios in both rodents and humans (Ito and Lee 2016). The ventral hippocampus, but not the dorsal hippocampus, exhibits increased power in the theta range (4–10 Hz) during conflict in

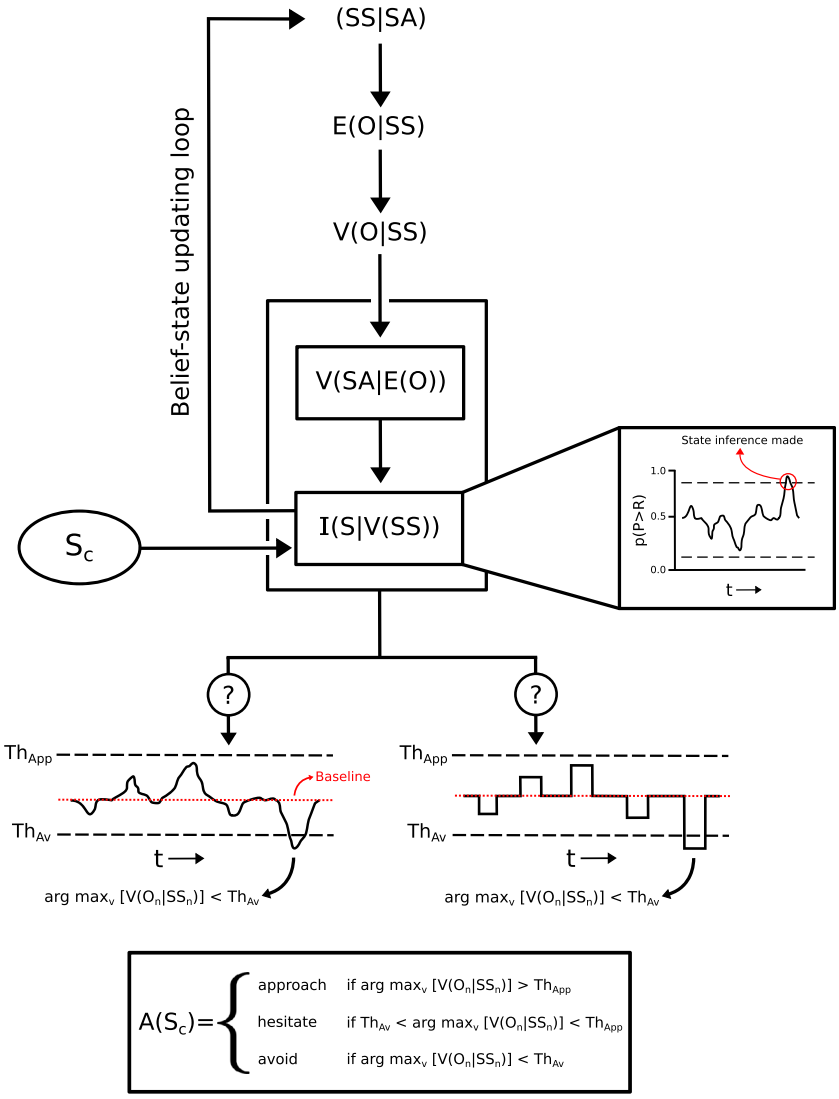

Fig. 6 Markov model of risky decision-making. During conflict, agents simulate action-state transitions, the expected contingencies of those states, the values associated with those contingencies, and ultimately the values associated with performing the simulated action that leads to that simulated state (SS). If the V(SA|E(O)) for a given SS fails to exceed a confidence threshold for making a state inference (see expanded view of I(S|V(SS)) which depicts threat-state monitoring, i.e., p(P > R) eventually passing a state inference threshold), the algorithm iterates through the belief-state updating loop until a state inference threshold is passed resulting in commitment to a decision. S_c, conflict state; S, state; A, action; SS, simulated state; SA, simulated action; E, expected; O, outcome; V, value; I, inferred; Th_{Av}, threshold for avoid decision; Th_{App}, threshold for approach decision

innately aversive contexts (Jacinto et al. 2016). In contrast, the dorsal hippocampus exhibits increased theta power during decisional uncertainty motivated by multiple competing tangible reinforcers such as is seen during both approach-approach conflict (Johnson and Redish 2007) and avoid-approach conflict (Kim et al. 2015). Furthermore, there are marked differences between simultaneously recorded dorsal and ventral hippocampal theta power, frequency, and coherence during a place-response strategy switching task involving working memory and spatial planning (Schmidt et al. 2013). These data suggest that the dorsal and ventral hippocampus have non-overlapping roles in responding to uncertain environments and that their dynamics might be sensitive to specific forms of conflict (e.g., innate, contextual conflict versus tangible, external conflict) dictated by the cognitive demands of the task. Altogether, these data highlight theta power as a valuable marker for identifying task-dependent neural signatures during reward-based, threat-based, and conflict-based tasks. However, the larger question of how decisional conflict is represented and sequentially processed neurobiologically, from state-outcome encoding to outcome valuation and action selection, remains unclear.

During periods of conflict, we hypothesize that the dorsal hippocampus simulates states using its map of the task space as a substrate for spatial planning. State inferences and state-outcome contingencies have been shown to be represented in orbitofrontal and anterior cingulate cortices (Sharpe et al. 2015; Hillman and Bilkey 2010; Cowen et al. 2012), and the ventral striatum and basolateral amygdala appear to be evaluating (and updating the stored value of) those contingency representations (Schoenbaum et al. 2003; Richard and Berridge 2011; Sugam et al. 2014; Sharpe and Schoenbaum 2016; Zalocusky et al. 2016; Lichtenberg et al. 2017). In rats, the prelimbic and infralimbic cortices are thought to play an important role in recalling task-specific conditioned responses (CRs) for the

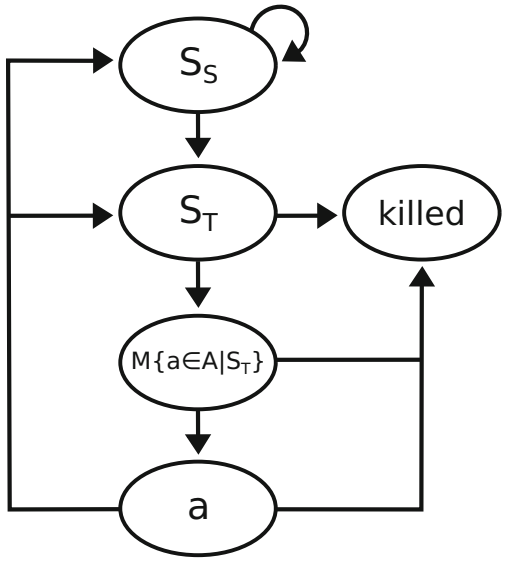

Fig. 7 Markov model of threat detection and evasion. The agent begins in a safe state (S_S) with no threat present. When the agent detects threat, it transitions from a safe state to a threat state (S_T). Following threat detection, the agent mobilizes for defensive behavior (M{a∈A|S_T}). An action (a) in the set of hard-wired, species-specific actions (A) is executed and the agent then transitions to one of three possible states: it is either captured and killed by the threat (killed), it remains in a state of threat, or it evades the threat and returns to a safe state. S_S, safe state; S_T, threat state; a, action; A, set of defensive behaviors; a∈A, action that exists in the set of defensive behaviors; M{a∈A|S_T}, mobilize for an action that exists in the set of defensive behaviors given the threat state

maintenance of optimal behavior during probabilistic decision-making (St. Onge and Floresco 2009; Zeeb et al. 2015), unlike orbitofrontal and anterior cingulate cortices which appear to be critical for learning the contingencies of a task and representing those environmental statistics for the purpose of cost-benefit calculations and conflict resolution (St. Onge and Floresco 2009; Zeeb et al. 2015). Specifically, it has been argued that prelimbic ensembles are storing motor-inhibitory CRs (e.g., freezing) while infralimbic ensembles are storing motor-excitatory CRs (e.g., suppression of freezing), possibly through the use of a mixed selectivity encoding scheme which allows for a computationally efficient distributed representation of a multitude of task-relevant variables (Grunfeld and Likhtik 2018). We suggest that it is this coordinated interaction between the dorsal hippocampus (state simulation), prefrontal cortices (contingencies and state-specific behaviors), and subcortical structures like the ventral striatum and basolateral amygdala (valuation) that underlies the cascade of representations triggered by decisional conflict.

Ethanol and diazepam: differences in pharmacokinetics and pharmacodynamics

Ethanol and diazepam both act as positive allosteric modulators at the $GABA_A$ receptor benzodiazepine binding-site. Unlike diazepam however, ethanol targets a variety of ion channel types and signaling systems (Crews et al. 1996; Lobo and Harris 2008), providing a possible explanation for why ethanol did not affect choice-point hesitation in the same way as diazepam. For example, ethanol is known to disrupt the hypothalamic–pituitary–adrenal axis as well as GABAergic, glutamatergic, opioidergic, and cholinergic neurotransmission (Rivier et al. 1984; Deitrich et al. 1989), any one of which could explain the behavioral differences seen between the two anxiolytics in our data. The finding that ethanol and diazepam had an anxiolytic effect on mid-track aborts and slow approach to threat is likely because both these behaviors rely on Pavlovian systems implemented by structures like the central nucleus of the amygdala and the periaqueductal gray (LeDoux and Daw 2018), both of which have been shown to be affected by ethanol and diazepam (Kang-Park et al. 2004; Jiménez-Velázquez et al. 2010; Roberto et al. 2012; Li et al. 2013). Interpreting our findings in the framework of our model, MTAs and slow approach to threat do not likely involve hippocampal-dependent state simulations whereas conflicted choice-point hesitation likely does.

This is supported by data showing an increase in the power of hippocampal theta oscillations during spatial planning (Johnson and Redish 2007) in addition to the well-documented ability of diazepam to attenuate the power of hippocampal theta (Yeung et al. 2012). Therefore, we suggest that diazepam is likely impairing the rats' ability to utilize their cognitive map of the task space for spatial planning resulting in prolonged indecision and an increase in risk-taking behavior resulting from a compromised ability to represent potential future threat, both of which are consistent with our data (Figs. 4 and 5).

Conclusion

While both ethanol and diazepam attenuated proximal-threat fear behavior, diazepam exclusively increased distal-threat hesitation and risky decision-making. Taken together, these data suggest that ethanol and diazepam act on non-overlapping threat processing circuits during avoid-approach conflict involving naturalistic threat and reward incentives. It is important for future research to be sensitive to the structure of the behavioral paradigms being used, how that structure influences which neural circuits are recruited to successfully navigate the task, and how that affects the generalizability of results obtained from tasks with differing behavioral and cognitive demands.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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References

Amir A, Lee S-C, Headley DB, Herzallah MM, Pare D (2015) Amygdala signaling during foraging in a hazardous environment. J Neurosci 35(38):12994–13005

Beck AT, Emery G and Greenberg RL (1985/2005), Anxiety disorders and phobias: a cognitive perspective, Basic Books

Blanchard DC, Blanchard RJ, Tom P, Rodgers RJ (1990a) Diazepam changes risk assessment in an anxiety/defense test battery. Psychopharmacology 101(4):511–518

Blanchard RJ, Blanchard DC, Weiss SM, Meyer S (1990b) The effects of ethanol and diazepam on reactions to predatory odors. Pharmacol Biochem Behav 35(4):775–780

Blanchard RJ, Magee LK, Veniegas R and Blanchard DC (1993) Alcohol and anxiety: ethopharmacological approaches., Progress in Neuro-Psychopharmacology & Biological Psychiatry, 17, 171, 182

Blanchard RJ, Yang M, Li C-I, Gervacio A, Blanchard DC (2001) Cue and context conditioning of defensive behaviors to cat odor stimuli. Neurosci Biobehav Rev 25(7–8):587–595

Bolles RC (1970) Species-specific defense reactions and avoidance learning. Psychol Rev 77(1):32–48

Choi J-S, Kim JJ (2010) Amygdala regulates risk of predation in rats foraging in a dynamic fear environment. Proc Natl Acad Sci 107(50):21773–21777

Cowen SL, Davis GA, Nitz DA (2012) Anterior cingulate neurons in the rat map anticipated effort and reward to their associated action sequences. J Neurophysiol 107(9):2393–2407

Crepeau L, Newman J (1991) Gender differences in reactivity of adult squirrel monkeys to short-term environmental challenges. Neurosci Biobehav Rev 15(4):469–471

Crews FT, Morrow AL, Criswell H and Breese G (1996) Effects of ethanol on ion channels, in International review of neurobiology, Vol. 39, Elsevier, pp. 283–367

Deitrich RA, Dunwiddie TV, Harris RA, Erwin VG (1989) Mechanism of action of ethanol: initial central nervous system actions. Pharmacol Rev 41(4):489–537

Dias BG, Banerjee SB, Goodman JV, Ressler KJ (2013) Towards new approaches to disorders of fear and anxiety. Curr Opin Neurobiol 23(3):346–352

Fanselow MS (1994) Neural organization of the defensive behavior system responsible for fear. Psychon Bull Rev 1(4):429–438

Fanselow MS and Lester LS (1988) A functional behavioristic approach to aversively motivated behavior: predatory imminence as a determinant of the topography of defensive behavior, in Evolution and Learning, ed R. C. Bolles and M. D. Beecher, 185-211

Ferreira V, Takahashi R, Morato G (2000) Dexamethasone reverses the ethanol-induced anxiolytic effect in rats. Pharmacol Biochem Behav 66(3):585–590

Gray J, McNaughton N (1982) The neuropsychology of anxiety. Oxford University Press in the press

Grewal SS, Shepherd JK, Bill DJ, Fletcher A, Dourish CT (1997) Behavioural and pharmacological characterisation of the canopy stretched attend posture test as a model of anxiety in mice and rats. Psychopharmacology 133(1):29–38

Grunfeld IS, Likhtik E (2018) Mixed selectivity encoding and action selection in the prefrontal cortex during threat assessment. Curr Opin Neurobiol 49:108–115

Hillman KL, Bilkey DK (2010) Neurons in the rat anterior cingulate cortex dynamically encode cost–benefit in a spatial decision-making task. J Neurosci 30(22):7705–7713

Ito R, Lee AC (2016) The role of the hippocampus in approach-avoidance conflict decision-making: evidence from rodent and human studies. Behav Brain Res 313:345–357

Jacinto LR, Cerqueira JJ, Sousa N (2016) Patterns of theta activity in limbic anxiety circuit preceding exploratory behavior in approach-avoidance conflict. Front Behav Neurosci 10:171

Jiménez-Velázquez G, López-Muñoz FJ, Fernández-Guasti A (2010) Parallel anxiolytic-like and antinociceptive actions of diazepam in the anterior basolateral amygdala and dorsal periaqueductal gray. Brain Res 1349:11–20

Johnson A, Redish AD (2007) Neural ensembles in CA3 transiently encode paths forward of the animal at a decision point. J Neurosci 27(45):12176–12189

Johnston AL, File SE (1991) Sex differences in animal tests of anxiety. Physiol Behav 49(2):245–250

Juavinett AL, Erlich JC, Churchland AK (2018) Decision-making behaviors: weighing ethology, complexity, and sensorimotor compatibility. Curr Opin Neurobiol 49:42–50

Kang-Park M-H, Wilson W, Moore S (2004) Differential actions of diazepam and zolpidem in basolateral and central amygdala nuclei. Neuropharmacology 46(1):1–9

Kim EJ, Kong M-S, Park SG, Mizumori SJ, Cho J, Kim JJ (2018) Dynamic coding of predatory information between the prelimbic cortex and lateral amygdala in foraging rats. Sci Adv 4(4):eaar7328

Kim EJ, Park M, Kong M-S, Park SG, Cho J, Kim JJ (2015) Alterations of hippocampal place cells in foraging rats facing a "predatory" threat. Curr Biol 25(10):1362–1367

LeDoux J (2012) Rethinking the emotional brain. Neuron 73(4):653–676

LeDoux J, Daw ND (2018) Surviving threats: neural circuit and computational implications of a new taxonomy of defensive behaviour. Nat Rev Neurosci 19:269–282

Li C, McCall NM, Lopez AJ, Kash TL (2013) Alcohol effects on synaptic transmission in periaqueductal gray dopamine neurons. Alcohol 47(4):279–287

Lichtenberg NT, Pennington ZT, Holley SM, Greenfield VY, Cepeda C, Levine MS, Wassum KM (2017) Basolateral amygdala to orbitofrontal cortex projections enable cue-triggered reward expectations. J Neurosci:0486–0417

Lobo IA, Harris RA (2008) GABAA receptors and alcohol. Pharmacol Biochem Behav 90(1):90–94

Maeng LY, Milad MR (2015) Sex differences in anxiety disorders: interactions between fear, stress, and gonadal hormones. Horm Behav 76:106–117

Miller NE (1944) Experimental studies of conflict, in personality and the behavior disorders, ed J M Hunt, 431-465

Mobbs D, Hagan CC, Dalgleish T, Silston B, Prévost C (2015) The ecology of human fear: survival optimization and the nervous system. Front Neurosci 9:55

Mobbs D, Kim JJ (2015) Neuroethological studies of fear, anxiety, and risky decision-making in rodents and humans. Curr Opin Behav Sci 5:8–15

Pare D, Quirk GJ (2017) When scientific paradigms lead to tunnel vision: lessons from the study of fear. npj Science of Learning 2(1):6

Prunell M, Escorihuela R, Fernandez-Teruel A, Nunez J, Tobena A (1994) Anxiolytic profiles of alprazolam and ethanol in the elevated plus-maze test and the early acquisition of shuttlebox avoidance. Pharmacol Res 29(1):37–46

Perusini JN, Fanselow MS (2015) Neurobehavioral perspectives on the distinction between fear and anxiety. Learn Mem 22(9):417–425

Richard JM, Berridge KC (2011) Nucleus accumbens dopamine/glutamate interaction switches modes to generate desire versus dread: d1 alone for appetitive eating but d1 and d2 together for fear. J Neurosci 31(36):12866–12879

Rivier C, Bruhn T, Vale W (1984) Effect of ethanol on the hypothalamic-pituitary-adrenal axis in the rat: role of corticotropin releasing factor (crf). J Pharmacol Exp Ther 229(1):127–131

Roberto M, Gilpin NW, Siggins GR (2012) The central amygdala and alcohol: role of γ-aminobutyric acid, glutamate, and neuropeptides. Cold Spring Harbor Perspectives in Medicine:a012195

Schmidt B, Hinman JR, Jacobson TK, Szkudlarek E, Argraves M, Escabí MA, Markus EJ (2013) Dissociation between dorsal and ventral hippocampal theta oscillations during decision-making. J Neurosci 33(14):6212–6224

Schoenbaum G, Setlow B, Saddoris MP, Gallagher M (2003) Encoding predicted outcome and acquired value in orbitofrontal cortex during cue sampling depends upon input from basolateral amygdala. Neuron 39(5):855–867

Sharpe MJ, Schoenbaum G (2016) Back to basics: making predictions in the orbitofrontal–amygdala circuit. Neurobiol Learn Mem 131:201–206

Sharpe MJ, Wikenheiser AM, Niv Y, Schoenbaum G (2015) The state of the orbitofrontal cortex. Neuron 88(6):1075–1077

St. Onge JR, Floresco SB (2009) Prefrontal cortical contribution to risk-based decision making. Cereb Cortex 20(8):1816–1828

Sugam JA, Saddoris MP, Carelli RM (2014) Nucleus accumbens neurons track behavioral preferences and reward outcomes during risky decision making. Biol Psychiatry 75(10):807–816

Treit D, Menard J, Royan C (1993) Anxiogenic stimuli in the elevated plus-maze. Pharmacol Biochem Behav 44(2):463–469

Wilson MA, Burghardt PR, Ford KA, Wilkinson MB, Primeaux SD (2004) Anxiolytic effects of diazepam and ethanol in two behavioral models: comparison of males and females. Pharmacol Biochem Behav 78(3):445–458

Wscieklica T, de Barros Viana M, Maluf LLS, Pouza KCP, Spadari RC, Céspedes IC (2016) Alcohol consumption increases locomotion in an open field and induces fos-immunoreactivity in reward and approach/withdrawal-related neurocircuitries. Alcohol 50:73–82

Yeung M, Treit D, Dickson CT (2012) A critical test of the hippocampal theta model of anxiolytic drug action. Neuropharmacology 62(1):155–160

Yokota S, Suzuki Y, Hamami K, Harada A, Komai S (2017) Sex differences in avoidance behavior after perceiving potential risk in mice. Behav Brain Funct 13(1):9

Zalocusky KA, Ramakrishnan C, Lerner TN, Davidson TJ, Knutson B, Deisseroth K (2016) Nucleus accumbens d2r cells signal prior outcomes and control risky decision-making. Nature 531(7596):642–646

Zeeb FD, Baarendse P, Vanderschuren L, Winstanley CA (2015) Inactivation of the prelimbic or infralimbic cortex impairs decision-making in the rat gambling task. Psychopharmacology 232(24):4481–4491