Exposure to extreme stress impairs contextual odour discrimination in an animal model of PTSD

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Abstract

Post-traumatic stress disorder (PTSD) patients respond to trauma-related danger cues even in objectively safe environments as if they were in the original event, seemingly unable to adequately modulate their responses based on the contextual cues present. In order to model this inability to utilize contextualized memory, in an animal model of PTSD, a novel experimental paradigm of contextual cue processing was developed – the differential contextual odour conditioning (DCOC) paradigm – and tested in trauma-exposed animals and controls. In the DCOC paradigm, animals encountered cinnamon odour in both an aversive environment and a rewarding (safe) environment. Response (freezing) to cinnamon odour was tested in a third, neutral environment to examine the ability of animals to modulate their responses based on the contextual cues. The effect of exposure to traumatic stressors, e.g. predator scent stress (PSS) and underwater trauma (UWT), on contextual cue discrimination was assessed. Rats trained in the DCOC paradigm acquired the ability to modulate their behavioural responses to odour cue based on contextual cues signalling safe vs. dangerous environment. The PSS and UWT stressors abolished the ability to modulate their responses based on contextual cues, both when exposure preceded DCOC training, and when it followed successfully completed training. The DCOC paradigm offers a promising model for studying the neurobiological basis of contextual modulation of response to potential threat in animals, a process that is disrupted by exposure to severe stress/trauma, and thus might be particularly salient for the study of PTSD.

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Introduction

Post-traumatic stress disorder (PTSD) is an incapacitating chronic syndrome involving cognitive, emotional and physiological failure to adequately process and/or recover from exposure to traumatic experience (APA, 1994). Exposure to trauma and the presence of intrusive symptoms – physiological hyperarousal and avoidance of traumatic reminders – are the core components of PTSD diagnosis. Clinically, PTSD patients relive their traumatic experiences repeatedly, unable to assimilate them as time- and context-limited events. For example, for a combat veteran, the sound of a passing helicopter in the current, objectively safe environment can evoke the traumatic experience of combat that took place years earlier. Deficient embedding or contextualization of the traumatic events in autobiographical memory is thought to be one of the main problems in PTSD (Ehlers and Clark, 2000).

Development of a valid animal model is an important step in elucidating neural mechanisms underlying PTSD; ultimately, the ‘optimal’ animal model should incorporate trauma-like exposure, will mimic pathophysiological and behavioural findings present in PTSD and will presumably involve...
neurobiological mechanisms that participate in PTSD pathophysiology. However, no single widely accepted animal model of PTSD has been established to date, and there is an ongoing debate over what constitutes a valid animal model for this disorder. Hence, there is no consensus as to whether the development of such a model should begin from replicating the trauma, replicating the neurobiological and behavioural characteristics or focusing on the presumed mechanisms. Animal ‘trauma’ includes models that address the intensity of the trauma and models concerned with its ethological relevance, e.g. focus on the aspect of a traumatic experience as a life-threatening event (Adamec et al., 2006a,b; 2007; Apfelbach et al., 2005; Blanchard et al., 2003; Blanchard and Blanchard, 1990; Blundell et al., 2005; Cohen et al., 1996, 1999, 2000, 2007a, 2008; Diamond et al., 2006; Endres et al., 2005; File et al., 1993; Kozlovsky et al., 2007a,b; Matar et al., 2006; Mazor et al., 2007; Richter-Levin, 1998; Roseboom et al., 2007; Sullivan and Gratton, 1998; Takahashi et al., 2005; Wang et al., 2000). Moreover, rodents show differential vulnerability to the lasting effects of predator scent stress (Bush et al., 2007; Cohen et al., 2003, 2004, 2005, 2006a–d, 2007a,b, 2008; Cohen and Zohar, 2004; Kozlovsky et al., 2007a,b; Matar et al., 2006; Mazor et al., 2007). However, it is not entirely clear what constitutes such an event in rodents.

Other animal models focus on modelling specific neurobiological sequelae or specific behavioural findings reported in PTSD. For example, the single prolonged stress (SPS) model was developed to mimic specific hypothalamic–pituitary–adrenal axis (HPA) abnormalities and enhanced acoustic startle (Khan and Liberzon, 2004; Liberzon et al., 1997, 1999a), whereas fear conditioning and extinction deficits have been proposed as the mechanism for PTSD re-experiencing symptom development (Blechert et al., 2007; Debiec and LeDoux, 2004, 2006; Garcia, 2002; Guthrie and Bryant, 2006; Maren, 2001; Maren and Chang, 2006; Milad et al., 2006, 2007a,b; Myers and Davis, 2002; Peri et al., 2000; Pittman et al., 2002; Quirk et al., 2006; Quirk and Mueller, 2007; Rauch et al., 2006; Shalev et al., 1992). The persistence of the psychological and biological fear responses could not be satisfactorily explained by the normative stress responses, leading some to suggest that fear conditioning might underlay the phenomenon (Pitman et al., 1993; Shalev et al., 1992). In certain respects, PTSD symptomatology resembles exaggerated fear conditioning (Milad et al., 2006); the traumatic event [unconditioned stressful stimulus (US)] triggers an unconditioned fear response (UR) which is characterized by strong arousal and intense fear. This UR becomes associated with cues, such as smells, voices, or sights [conditioned stimulus (CS)] which were present during the traumatic event. As a result of this pairing, these cues can trigger similar responses even in the absence of the US (Blechert et al., 2007; Yehuda, 2004). Since conditioned fear responses can be extinguished by repeatedly presenting the CS without the US (Milad et al., 2006), impaired extinction learning has been proposed as an alternative mechanism for the formation of PTSD symptoms (Blechert et al., 2007; Guthrie and Bryant, 2006; Maren and Chang, 2006; Myers and Davis, 2002). It has been established that fear extinction is dependent on NMDA receptors and L-type voltage-gated calcium channels (Cain et al., 2002; Falls et al., 1992); is sensitive to modulation of second-messenger systems, including kinase and phosphatase activity (Szapiro et al., 2003); and may require protein synthesis (Davis et al., 2006; Lattal and Abel, 2001; Santini et al., 2004). Recently, a prominent role for medial prefrontal cortex (mPFC)–amygdala–hippocampus circuits has been suggested in the contextual modulation of the extinction of fear memory (Liberzon and Sripada, 2008). The current neurocircuitry model for PTSD hypothesizes hyper-responsivity within the amygdala to threat-related stimuli, with inadequate top-down governance over the amygdala by mPFC (encompassing the rostral anterior cingulated cortex, subcallosal cortex, anterior cingulated cortex), orbitofrontal cortex and the hippocampus (Rauch et al., 2006). The decreased mPFC inhibition of the amygdala prevents retention of extinction learning, thus allowing reinstatement of the conditioned fear response. Interestingly, neuroimaging data support the current neurocircuitry model of PTSD and provide evidence for heightened responsivity of the amygdala, diminished responsivity of the mPFC, diminished hippocampal volumes and integrity, as well as impaired hippocampal function in PTSD (De Bellis et al., 2000, 2002; Etkin and Wager, 2007; Freeman et al., 1998; Lanius et al., 2001; Liberzon et al., 1999b; 2003, 2007; Liberzon and Sripada, 2008; Rauch and Shin, 1997; Rauch et al., 1996, 2000, 2006; Semple et al., 1996, 2000; Vermetten and Bremner, 2002). However, PTSD is a complex disorder that involves far more than an exaggerated fear response, and cannot be explained by a simple conditioning model.

A different mechanism that may contribute to the development of PTSD symptoms is the inability to appropriately ‘contextualize’ the traumatic events in autobiographical memory. Inability to use contextual information (safety signals) to modulate behavioural response to a potentially threatening event could lead
to the myriad of behavioural symptoms experienced by PTSD patients. Indeed, a suggestion of contextual memory deficits has been reported in the SPS animal model of PTSD (Khan and Liberzon, 2004; Liberzon et al., 1997, 1999a); however, direct testing of contextual cue-processing is required in order to reliably demonstrate inability to contextualize memory in PTSD animal models. To this end, a novel experimental paradigm was devised [differential contextual odour conditioning (DCOC)], in order to examine the ability of animals to discriminate, in a novel, neutral environment, the contextual significance of an odour cue acquired in both safe and dangerous environments. The effects of exposure to traumatic stress [predator scent stress (PSS), underwater trauma (UWT)] on the ability to contextualize odour cues were then assessed. Furthermore, in order to verify that deficits in the ability to contextualize are indeed associated with a traumatic experience and are not merely a response to stress, the impact of exposure to the above traumatic stress protocols was compared to that of exposure to stressful but not traumatic protocols, i.e. elevated platform (EP) stress and 1-h restraint stress (RST).

Materials and methods

All procedures were carried out in strict compliance with ethical principles and guidelines of the NIH Guide for the Care and Use of Laboratory Animals. All treatment and testing procedures were approved by the Animal Care Committee of Ben-Gurion University of the Negev, Israel.

Animals

Two-hundred and nine adult male Sprague–Dawley rats weighing 180–200 g were employed. Animals were habituated to the housing conditions for at least 10 d, and during this time handled once daily, i.e. picked up with a gloved hand. The animals were housed four per cage in a vivarium with stable temperature and a reversed 12-h light/dark cycle (lights off 08:00 hours). All testing was performed during the dark phase of the animals between 09:30 and 17:00 hours. Experiments were designed to minimize the number of animals tested. Animals in a given experiment, depicted in the respective schematic illustrations, derived from the same batch and were tested simultaneously.

DCOC

To test ability of animals to learn and remember contextual cues, a contextual odour conditioning paradigm was devised. It consists of a cue, cinnamon odour, that could signal reward or punishment (safety or threat signal) depending on the contextual cues present. Rats were exposed to the cue (cinnamon odour) + reward (sweetened water) in arena 1, and to cue + conditioned cue (80 dB tone) + aversive unconditioned stimulus (electric shock) in arena 2. These two conditions were learned in two separate chambers in different rooms. In order to ensure that the odour stimulus was only a part of the contextual environment and not the primary stimulus conditioner, animals were exposed to an auditory tone as a CS in the foreground contextual conditioning. In this way, the odour stimulus remained as part of the context in the background conditioning scheme. The animals were tested in a third neutral chamber (arena 3) where only the cinnamon odour contextual cue was presented. [After training, part of the animal population was additionally tested in the aversive arena (arena 2; expt 1) and in the neutral arena (arena 3) when the odour stimulus was removed (expt 3).]

Set up

Three highly distinctive arenas were used, considerably different in shape, surface texture and construction material:

Arena 1. A hexagonal prism made of perspex with transparent side walls and a 10-cm-long side arm with a guillotine door at its end; this arena was dedicated to positive (appetitive) conditioning.

Arena 2. A rectangular arena with two metal walls and two Plexiglas walls, and a grid floor; this arena was used for negative (aversive) conditioning.

Arena 3. A testing chamber (neutral) comprising a wooden square with sawdust bedding; this chamber was used for the evaluation of contextualization.

Experimental procedures

Prior to training, rats were maintained on a 16-h water-deprivation schedule with food available ad libitum.

DCOC procedure

One hour before the experiment, the cinnamon odour (commercial odours that are regularly used in the cosmetics and food industries) was burned using a standard candle-lit burner for aromatic oils. The candle was extinguished before the behavioural experiment and an additional three drops of the aromatic oil was added to the unlit burner.
Appetitive conditioning (arena 1). In the presence of the odour cue, a feeding bottle of sweet water was presented through the door as the reward. Training duration was 7 min, consisted of one trial per day for 10 consecutive days. Time until the animal started drinking was measured and subsequently used as a dependent variable. Animals were returned to their home cages after drinking for 60 s.

Aversive conditioning (arena 2). After 2 min for acclimatization, in the presence of odour cue (cinnamon), a 10-s tone (80 dB, 9 kHz sine wave, 10 ms rising and falling time) was presented that co-terminated with the start of a scrambled electric footshock of 10-s duration (0.85 mA). The conditioning procedure was repeated five times with inter-tone intervals between 110 s and 140 s. Training consisted of one trial per day, for 5 consecutive days, beginning at day 6 of the appetitive conditioning. Animals were returned to their home cages 60 s after the last footshock.

Testing (arena 3). Freezing behaviour was recorded using an overhead video camera and scored for immobility (freezing) using the recorded images. The videotape and the recorded images were both scored by a trained observer unaware of the treatment conditions. Freezing behaviour was defined as the absence of all movements except for those related to respiration (Kim and Fanselow, 1992), and was assessed for 6 min in the presence of the odour cue alone. Total cumulative freezing time (total seconds spent freezing during each assessment period) was measured and calculated as a percentage of total time.

Control condition: contextual odour conditioning (COC)

All procedures were identical for the aversive and neutral arenas (2 and 3) whereas in the appetitive arena (1), conditioning was performed without the cinnamon odour, i.e. only the sweet water reward/reinforcement.

Stress exposure

Predator scent stress (PSS). This consisted of placing the test animals on well-soiled cat litter (in use by the cat for 2 d, sifted for stools) for 10 min in a closed environment (i.e. inescapable exposure). Exposure of rodents to PSS is fear provoking and very stressful in situations where both ‘fight’ and ‘flight’ options are not available. PSS has ecological validity in that it mimics intense threatening experiences with lasting affective consequences (Adamec et al., 2006a,b; 2007; Cohen et al., 1996, 2000, 2003; Cohen and Zohar, 2004). The control animals (sham) were exposed to identical fresh, unused litter for the same amount of time.

Underwater trauma (UWT). Animals were given 1 min to swim in a circular pool (1.8 m diam, 0.6 m high), containing water at 26±1 °C and then held under water for 30 s using a metal net. Control rats were given 1 min to swim and then were put back in their resting cage (Cohen et al., 2007a; Richter-Levin, 1998; Wang et al., 2000).

Restraint stress (RST). Animals were restrained in a wire mesh cage (Natsume, Japan) for 1 h prior to experimentation. The restraint was such that the rats could only move slightly (to turn in the direction of their body only) (Armario et al., 2004).

Elevated platform stress (EP). Animals were placed on an elevated platform (12 × 12 cm) for 30 min in a brightly lit room (Maroun and Richter-Levin, 2003).

Experimental design

Three studies were conducted. The first study assessed the effects of DCOC procedure on freezing behaviour (n=68) (Figure 1). Rats were randomly assigned to two groups: DCOC and COC (n=17 each group). On day 11, freezing behaviour (to cinnamon odour) was tested in the neutral arena (arena 3). In order to test the ability of the rats to adequately respond to the odour stimuli alone in the aversive context they began DCOC training as described. Then on day 11 freezing behaviour was tested in the aversive arena (without tone and electric footshock) (arena 2; Figure 2). Rats were randomly assigned to two groups: DCOC and COC controls (n=17 each group). In the second experiment, we tested the effects of pre-training exposure to traumatic stressors on the animal’s ability to learn to differentiate contextual cues, using the DCOC procedure (n=108) (Figure 3). Animals were divided into five groups and underwent one of four different types of stress exposure; 1 d later, animals began DCOC training. The control (naive) group underwent DCOC training without stress pre-exposure. Animals were tested in arena 3 on day 11. The effects of pre-training exposure to traumatic stressors on the animal’s ability to learn to differentiate contextual cues were also assessed in the neutral arena (arena 3) excluding odour stimuli as a contextual element. Rats were randomly assigned to two groups: (n=15 each group) naive DCOC and PSS-DCOC. On day 11, freezing behaviour (without cinnamon odour)
was tested in the neutral arena (arena 3; Figure 4). In the third experiment (n = 33) (Figure 5), we investigated the effects of stress exposure following DCOC procedure on the ability to differentiate contextual cues. Animals underwent stress exposure 2 d after DCOC training, on day 12 of the protocol. Animals were tested in arena 3 on both day 11 (before stress) and on day 19 (7 d after stress).

To control for experiential procedure differences, all tests were performed at the same time of day. Furthermore, control animals were transferred from the vivarium to an adjacent room for the same period of time as were test subjects.

**Statistical analyses**

Freezing time and time until the animal started drinking were analysed using repeated-measures analysis of variance (ANOVA). If significant effects were found, post-hoc Bonferroni test was used to examine differences between individual groups. The areas under the curve (AUCs) were calculated by the trapezoidal rule.

In expt 3 the behavioural data from the UWT control group, as well as the PSS control group, were compared to the naive (unexposed) group. Since we found no significant differences between the groups, the data from all the control groups were compiled into one control group (‘naive’ group).

**Results**

**DCOC**

Freezing behaviour was analysed using repeated-measures ANOVA; measurements were made in five blocks of 1-min each in the neutral (arena 3) arenas for both DCOC and COC animals, and are shown in Figure 1(a, b).

DCOC rats displayed significantly less immobility in the neutral arena than COC animals. Repeated-measures ANOVA showed an effect for group \( F(1, 32) = 174.4, p < 0.0001 \), a time effect \( F(4, 128) = 16.4, p < 0.0001 \) and a group × time interaction effect \( F(4, 1428) = 3.8, p < 0.006 \). Post-hoc Bonferroni test revealed that DCOC rats displayed significantly less immobility than COC rats (p < 0.0001 for all time-points). Similar results were obtained when examining the AUCs that present the results of testing in arena 3 (AUCs in Figure 1b). DCOC subjects exhibited a
lower level of freezing behaviour over the 5-min testing session compared with the COC rats \((p < 0.0001)\). Together the results indicate that DCOC animals indeed learned to dissociate between the presence of the odour in different contexts while acquiring the conditioning response to the aversive context.

**Freezing in the aversive arena**

Freezing behaviour was analysed using repeated-measures ANOVA; measurements were made in five blocks of 1-min each in the aversive (arena 2) for both DCOC and COC animals, and are shown in Figure 2(a, b). Both DCOC and COC groups exhibited similarly high levels of freezing, demonstrating intact contextual fear conditioning learning in both groups \([\text{group}: F(1, 32) = 3.9, p = 0.07; \text{time}: F(4, 128) = 0.6, p = 0.7; \text{group} \times \text{time interaction}: F(4, 128) = 0.3, p = 0.9]\).

**The effects of pre-training stress exposure on freezing responses**

As shown in Figure 3(a, b), immobility in the neutral arena in the presence of the conditioned odour cue differed significantly among the groups. PSS and UWT stress experience before DCOC training completely eliminated the ability of the animals to demonstrate DCOC. From the 3rd minute onward, PSS and UWT groups exhibited significantly more freezing than DCOC animals that were not pre-exposed to stress \((p < 0.0001\) for PSS and UWT groups vs. naive). In general, RST and EP stress protocols led only to a transient, rapidly decaying freezing response; EP and RST animals were not different from non-pre-exposed animals. Repeated-measures ANOVA revealed a significant effect for group \([F(4, 73) = 59.3, p < 0.0001]\), a significant time effect \([F(4, 292) = 41.7, p < 0.0001]\), and a significant interaction between group and time \([F(16, 292) = 2.5, p < 0.002]\). The PSS stressor elicited significantly longer periods of immobility than UWT, RST and EP stressors \((p < 0.0001\) for all time periods). Figure 3b depicts the AUC for testing of all groups.

As shown in Figure 4(a, b), immobility in the neutral arena excluding odour stimuli and contextual elements did not differ among the groups. Both DCOC and COC groups exhibited similarly low rates of freezing, demonstrating that in the absence of the odour stimulus no freezing was observed \([\text{group}: F(1, 28) = 0.45, p = 0.5; \text{time}: F(4, 112) = 23.4, p < 0.0001; \text{group} \times \text{time interaction}: F(4, 112) = 0.3, p = 0.87]\).
The effects of post-training stress exposure on freezing responses

Baseline assessments

Freezing behaviour of DCOC-exposed and COC animals at baseline (pre-stress exposure) in the neutral arena in the presence of the conditioned odour cue was analysed by repeated-measures ANOVA, in five blocks of 1-min each (Figure 5). ANOVA revealed a significant effect for group \(F(1, 15) = 369.5, p < 0.0001\), and a significant time effect \(F(4, 60) = 9.7, p < 0.0001\). At baseline, post-hoc Bonferroni revealed that the COC rats displayed significantly more immobility than the naive DCOC group (\(p < 0.0001\) for all time-scales) (Figure 5a,c), thus confirming the previous results (Figure 1).

PSS after DCOC training

When animals were exposed to stress after DCOC training and tested in the DCOC paradigm 7 d after the stress, PSS exposure impaired the ability of animals to retain differential odour conditioning. The freezing response in arena 3 was significantly longer in the PSS-DCOC and PSS-COC animals than in the non-exposed (sham) animals. Repeated-measures ANOVA revealed a significant effect for group \(F(3, 13) = 37.8, p < 0.0001\), a significant time effect \(F(4, 52) = 6.1, p < 0.0005\) and a significant group \(\times\) time interaction \(F(12, 52) = 2.7, p < 0.008\) (Figure 5b). Post-hoc Bonferroni test showed a significant difference between exposed vs. non-exposed groups (\(p < 0.0001\) for DCOC and \(p < 0.015\) for COC). The freezing response was significantly longer in the sham-COC than in the sham-DCOC group (\(p < 0.007\)). PSS-COC rats exhibited significantly longer periods of immobility than the PSS-DCOC rats (\(p < 0.04\) (Figure 5c).

Discussion

We have developed an experimental paradigm (DCOC) that allows us to examine the ability of the animal to modulate response to a potentially dangerous environmental cue based on the contextual information. We then assessed the effects of traumatic stress exposure on the ability of animals to distinguish
between the environmental context in which an odour cue was previously encountered and the significance of the same cue in an unfamiliar, neutral test environment.

Animals exposed to a stimulus (odour) coupled with both an aversive stimulus in one environmental context and with reward in a different context responded to the same odour stimulus in a neutral test environment with less fear (no freezing response) than rats exposed to the odour stimulus only in the aversive environmental context. Two aspect of the process of contextualization were thus demonstrated in this paradigm. Rats trained only in the aversive context successfully linked the odour encountered in an unfamiliar environment to the context of threat, demonstrating their contextualization of an environmental cue (conditioning). Rats exposed to the odour cue in both aversive and rewarding contexts were able to distinguish the significance of an isolated cue in the context of a novel environment, per se. The DCOC paradigm thus appears to assess the ability to distinguish the contextual significance of an isolated cue in a valid manner.

Exposure to a significant stress markedly affected this ability. In the presence of the odour cue, stress-exposed animals displayed marked freezing in the novel environment, whether they had successfully completed DCOC training before the stress or whether they underwent training after the stress. In the absence of the odour stimulus no freezing was observed, as repeatedly reported by Adamec and colleagues (Adamec and Shallow, 2000; Blundell et al., 2005). Thus, once traumatized, the animals responded to the odour cue as indicating a threat, despite the fact that it had also been encountered in a rewarding context, and were unable to distinguish between the isolated cue and its contextual significance. The extent of the disruption of contextual cue distinction was determined by the character of the stress paradigm to which the rats had been exposed. The PSS and UWT paradigms caused extreme, long-term disruptions, whereas the EP and RST paradigms caused relatively minor and temporary disruptions. Thus, the response appears to reflect the relative ‘potency’ of the stressor, lending further support to a link between traumatic stress and disrupted contextual cue distinction.

![Diagram](https://via.placeholder.com/150)

**Figure 4.** Pre-training stress-exposure caused both differential contextual odour conditioning (DCOC) animals and contextual odour conditioning (COC) groups to exhibit similar low rates of freezing in the neutral arena (arena 3) excluding odour stimuli. Panel (1): The behavioural procedure used during training for both control and stress-exposed animals. (a) Freezing response in the neutral arena excluding odour stimuli after pre-training stress exposure. (b) The area under the curve (AUC) for testing in the neutral arena excluding odour stimuli after pre-training stress exposure. PSS, Predator scent stress. All data represent group mean ± S.E.M.
variety in the degree of behavioural responses demonstrated by the DCOC paradigm demonstrates that the test paradigm is quite sensitive and lends it face validity.

Hypothetically contextualization would involve interplay of the psychological constructs mentioned above (i.e. fear conditioning, extinction, and learning). The importance of the mPFC, amygdala, and hippocampus in these psychological constructs raises the possibilities that contextualization is dependent on the integrity of the mPFC, amygdala, and hippocampus; and PSS induced deficits in contextualization mediated, in part, by PSS-induced changes in neural transmission in these brain substrates (Kohda et al., 2007; Liberzon et al., 1997; Liberzon et al., 1999a).

Cognitive theorists propose that memories of experiences are represented in structures that act to cluster together related information, e.g. contextual frames (Bar, 2004; Bar and Aminoff, 2003; Mobbs et al., 2006). One contextual frame may represent ‘kitchen’, whilst another represents ‘office’, or ‘street’, and they influence how one perceives, predicts and responds to the environment (Bar, 2004; Mobbs et al., 2006). New information appears in an existing contextual frame, is processed and integrated, updating the frame by adding new associations, and/or removing those that become irrelevant over time (Bar, 2004). From an evolutionary standpoint, this process would improve ‘fitness’ by optimizing predictions of imminent threat by streamlining search within memory (Bar, 2007; Mobbs et al., 2006), such that if threat was previously encountered, the individual will behave more watchfully in similar contexts, thus increasing its chances of avoiding the threat and of surviving. Characteristically, trauma-related stimuli act as potent cues, disproportionately arousing psychophysiological responses in PTSD patients. This pattern of response tends to undergo a progressive generalization to include additional stimuli, especially unpredictable, unfamiliar and/or uncontrollable situations.

Figure 5. Post-training stress-exposure on freezing responses in the neutral arena (arena 3) was significantly longer in the predator scent stress-differential contextual odour conditioning (PSS-DCOC) group and PSS-COC group than in the control sham (clean litter exposed) animals. Panel (1): The behavioural procedure used during training for both control and stress-exposed animals. (a) Freezing response in the aversive arena at baseline. (b) Freezing response in the neutral arena 7 d after post-training stress exposure. (c) The area under the curve (AUC) for testing in arena 3. All data represent group mean \pm S.E.M.
Overall, this difficulty with assessing the isolated stimulus and its significance within the current context indicates that the innate flexibility required for an ongoing contextual updating process and the concomitant fine tuning of adequate responses might be diminished. Thus, the sound of a helicopter over one’s home town or the smell of a neighbour’s barbecue are related to by the patient within the threatening contextual frame of combat, rather than the current, neutral context within which they are encountered. A recent report by Gilbertson and colleagues (2007) lends additional clinical evidence for contextualization impairment in chronic PTSD patients. In this study, PTSD combat veterans demonstrated significantly impaired performance in configural spatial processing relative to non-PTSD combat veterans, specifically in tasks that required perception of ‘allocentric’ (as opposed to ‘egocentric’) spatial context. Deficits were significantly related to PTSD severity and to hippocampal volume.

It is important to note here that some caution has to be exercised in interpretation of the results of the novel paradigm presented here. First, the olfactory stimuli are known to be very potent and the paradigm was thus intentionally based on olfaction stimulus at this stage. Other types of stimuli – auditory, tactile and visual – will be important to examine in the future, for better understanding of stimulus contextualization. Furthermore, the process of contextualization as discussed herein appears to have been modelled validly by the DCOC paradigm. However, it represents only one approach to interpreting the clinical phenomenon of disproportionate responses to overly generalized, isolated trauma cues, although other conceptual approaches exist and no single approach can aspire to be all-embracing.

Conclusions

The novel DCOC paradigm presented here appears to model the ability to modulate behavioural responses to potentially threatening cues with face validity in rodents. Severe or ‘traumatic’ stress exposure prior to or following DCOC abolished the ability of animals to contextualize the odour cue when encountered in a different environment. Thus, the DCOC paradigm is suggested as an effective animal model that can enable the study of the neurobiology of contextualization and of related pathology.

Statement of Interest

None.

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