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Repeated unpredictable threats without harm impair spatial working memory in the Barnes maze

Diane J. Kim [a], Nathan St. Louis [a], Ralph A. Molaro [a], Glenn T. Hudson [a], Robert C. Chorley [a], Brenda J. Anderson [a,b,*]

[a] Dept. of Psychology, State University of New York at Stony Brook, Stony Brook, NY 11794-2500, United States
[b] Program in Neuroscience, State University of New York at Stony Brook, Stony Brook, NY 11794-2500, United States

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ABSTRACT

Psychological stressors elicit the anticipation of homeostatic challenge, whereas physical stressors are direct threats to homeostasis. Many rodent models of stress include both types of stressors, yet deficits, like those reported for working memory, are often attributed to psychological stress. To empirically test whether intermittent psychological stressors, such as repeated threats, are solely sufficient to impair spatial working memory, we developed a novel rodent model of stress that is restricted to the anticipation of threat, and free of direct physical challenge. Adolescent male Sprague-Dawley rats were randomly assigned to control (CT) or stress (ST) housing conditions consisting of two tub cages, one with food and another with water, separated by a tunnel. Over three weeks (P31–P52), the ST group received random (probability of 0.25), simultaneous presentations of ferret odor, and abrupt lights, and sound at the center of the tunnel. Relative to the CT group, the ST group had consistently fewer tunnel crossings, consistent with avoidance of a psychological stressor. Both groups had similar body weights and crossed the tunnel more in the dark than light period. Three days after removal from the treatment conditions, spatial working memory was tested on the Barnes maze. The ST group displayed deficits in spatial working memory, including longer latencies to enter the goal box position, and a greater number of returns to incorrect holes, but no significant differences in speed. Memory can be affected by sleep disruption, and sleep can be affected by stress. Circadian activity patterns in the tunnels were similar across groups. Therefore, the data suggest that intermittent threats without physical stress are sufficient to impair spatial working memory in adolescence.

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1. Introduction

An organism attempts to uphold a steady equilibrium despite a constantly changing environment. When that equilibrium is at risk, a general physiological response, the stress response, serves to restore it. The most basic stress response is a *reactive* response (*a feedback control strategy*) to *physical stressors*, which are direct challenges to homeostasis (Herman, Prewitt, & Cullinan, 1996; Sawchenko, Li, & Ericsson, 2000). Direct challenges include any phy siological/systemic/interoceptive triggers, including changes in temperature, oxygen availability, hypoglycemia, dehydration, and injury (Ulrich-Lai & Herman, 2009). Indirect threats such as stress related to work (i.e. job insecurity, role overload, etc.) (Gilboa, Shirom, Yitzhak, & Cooper, 2008), threats of traumatic events (i.e. terrorism, violence, and natural disasters) (Cancro, 2004; Cohen & Eid, 2007), or social conflict (Miller, 2007) require cognitive interpretation of cues, perceived and processed bv higher order brain regions (Jankord & Herman, 2008; Sawchenko et al., 2000), that in turn serve as predictors of homeostatic challenge. The remoteness of the physical stressor allows feedforward control mechanisms to produce *anticipatory/psychological/proactive/proces sive* stress responses in addition to behavioral responses (e.g., risk assessment and avoidance) that serve to prevent or prepare for harm.

Humans are uniquely vulnerable to anticipatory stressors, because of their ability to anticipate events far in the future. Mason (1968) concluded that psychological stressors are "among the most potent natural stimuli" to produce a stress response. Stress in adolescence is known to increase risky decision making, but the types and frequency of stressors that contribute to these outcomes are difficult to parse in human studies (Galvan & Rahdar, 2013). For example, investigating the role threats, such

* Corresponding author at: Dept. of Psychology, 100 Nicolls Road, State University of New York at Stony Brook, Stony Brook, NY 11794-2500, United States.
E-mail address: Brenda.Anderson@stonybrook.edu (B.J. Anderson).

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as exposure to neighborhood violence, play in shaping behavior is difficult because neighborhood violence is strongly associated with other factors such as poverty, social cohesion and disorder. Thus to fully understand whether threat by itself is sufficient to drive changes in behavioral tendencies, including memory, we need experimental approaches that utilize animal models. In the present study, we are focusing on behavioral effects at developmental time points proximal to the stressors in order to understand how the environment shapes ongoing behavioral tendencies in adolescence and young adulthood.

Adolescence is a time when animals gain independence, which brings increased exposure to risk. During foraging, memory for high resource locations, and a cognitive map supporting the relationship between current location and the safe space of a nest are critical in environments with high risk for predation. Adolescence is also a time in which structures critical for memory continue to mature (McCormick & Mathews, 2010), including substantial growth of hippocampal pyramidal cell dendrites and spines (Chowdhury, Barbarich-Marsteller, Chan, & Aoki, 2014). Stress has often been reported to impair memory, which, in the context of foraging, would be maladaptive. Here, we set out to reproduce the threats faced during foraging and test whether threats without harm are sufficient to produce memory deficits in adolescent rats.

We have previously shown that exposure to repeated threats increases defensive responding without affecting symptoms associated with depression (Kim & Anderson, 2015). Stress has been proposed to prioritize habitual responses and defense responses over cognitively demanding responses (Arnsten, 2009; Dias-Ferreira et al., 2009; Schwabe, Dalm, Schachinger, & Oitzl, 2008; Taylor et al., 2014). Accordingly, it is possible that exposure to repeated threats will impair spatial memory. Such deficits would parallel previous reports that chronic stress impairs spatial working memory (Conrad, Galea, Kuroda, & McEwen, 1996; Kleen, Sitomer, Killeen, & Conrad, 2006; Luine, Villegas, Martinez, & McEwen, 1994), although many of those studies used stress models that may include physical stressors.

To understand the behavioral consequences of intermittent anticipatory stress resulting from threats without accompanying direct, physiological challenges, we developed a semi-naturalistic rodent foraging environment that includes the repeated, intermittent presentation of threats that are unpredictable in timing and without deliverance of direct harm or pain. The threat stimuli (abrupt sound, light and predator odor) are presented in the central location of a tunnel that must be crossed to obtain food and water, which are placed on opposite ends of the tunnel. The stimuli are presented when the animal is detected at the central location, but occur unpredictably with a probability of 0.25. By using ferret dander odor and abrupt auditory and visual stimuli, the model incorporates the dependency on exteroceptive cues and higher order processing for awareness of the potential for harm, and therefore the need for pre-emptive activation of the stress response. The model was designed to center around the ability of predator dander odor, specifically that of ferret dander, to signal impending threat (Masini, Sauer, & Campeau, 2005; Masini, Sauer, White, Day, & Campeau, 2006) activate the HPA axis (Masini et al., 2005), initiate c-fos expression and elicit defense behaviors (Masini et al., 2005), but uses abrupt stimuli to increase the complexity of the threat in order to avoid habituation. Previous work from our lab has shown that these simultaneously presented stimuli predictably and persistently elicit risk assessment behaviors (Kim & Anderson, 2015), including stretch-attending, head scanning, and passive avoidance. Thus the model allows for the induction of anticipatory stress within a semi-naturalistic living habitat that includes a foraging feature. By presenting the threats in the center of the tunnel midway between food and water, the subjects faced an approach-avoidance conflict that is inherent to the foraging environments navigated by most species, including humans. The events within the habitat can be controlled by the investigator (e.g., the probability of threats) and therefore are similar for all rats in the condition unlike events in the visible burrow system (Blanchard & Blanchard, 1989; Blanchard, Dulloog, et al., 2001; Blanchard, Yudko, Dulloog, & Blanchard, 2001; Blanchard et al., 1995; Davis, Krause, Melhorn, Sakai, & Benoit, 2009) where innate individual differences produce dominant and subordinant groups. Further, in the present paradigm, individual behavioral responses are automatically recorded for each individual. Thus, the model has ethological features, provides the ability to apply threat, and provides the ability to monitor responses without human contact.

In the present study we seek to test whether anticipatory stress can affect spatial memory. Chronic stress is reported to have fewer effects on memory tested in aversive rather than neutral conditions (Conrad, 2010), therefore we tested spatial memory in neutral conditions. The Barnes Maze (Barnes, 1979) allows for testing spatial memory without the physical challenge of deprivation, and therefore avoiding testing in stressful conditions. Although the Barnes Maze is not highly arousing, the rats are motivated to find the dark goal box in order to escape from the open circular platform in a bright room. Chronic stress has also been shown to inhibit increases in locomotion and exploration produced by conditions of novelty (Blanchard, Kelley, & Blanchard, 1974; Conrad, LeDoux, Magarinos, & McEwen, 1999; Katz, Roth, & Carroll, 1981), although the effects are mixed (Wright & Conrad, 2005). Since speed could influence memory by reducing the time over which the holes already visited have to be remembered, we also measured speed in the maze. We hypothesize that the three-week exposure to intermittent threat will impair spatial working memory. Rats were subjected to the treatment conditions between p31 and p 52, a time period that corresponds to the end of early adolescence through the middle of late adolescence/young adulthood (Tirelli, Laviola, & Adriani, 2003), therefore the treatment covers a large span of the adolescent stage.

Stress can affect sleep cycles (Cheeta, Ruigt, van Proosdij, & Willner, 1997), and after exposure to a predator, rats can sleep less (Lesku et al., 2008). While sleep enhances memory (Colgin & Moser, 2006; Lee & Wilson, 2002), sleep fragmentation and disruption impair spatial learning (Ferrara et al., 2006, 2008; Peigneux et al., 2004; Wallace et al., 2015). Hence, a model that includes predator threat may disrupt sleep which, in turn may disrupt memory. Although it would be difficult to measure sleep in our model, it is possible to measure circadian activity cycles. If cycles are disrupted, any deficits in memory could be potentially attributed to sleep disruption. Thus, we also measured activity in the tunnels over the course of the day during the experimental conditions.

2. Methods

2.1. Subjects

Male Sprague-Dawley rats were born to dams (Taconic Farms, http://www.taconic.com/) in the local animal facility, weaned on PND 21 and transferred to our colony at PND22. Animals were housed in a reversed light-dark cycle. The rats were handled for one week and then randomly assigned to two separate conditions: control group (CT) (n = 13) and stress group (ST) (n = 9).

2.2. Apparatus and experimental conditions

Tunnels (91 cm long) consisted of an aluminum lane (15.9 cm wide) covered with hardware cloth separating two standard tub

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