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Research report

Alterations in cognitive flexibility in a rat model of post-traumatic stress disorder

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HIGHLIGHTS

- Single prolonged stress (SPS) leads to complex alterations in flexible responding.
- SPS did not impair acquisition of either a response or visual-cue discrimination.
- SPS rats made more perseverative errors during a reversal-type shift.
- SPS rats were impaired at selecting a novel strategy during strategy set-shifting.
- Executive function deficits in PTSD may be a consequence of trauma exposure.

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ABSTRACT

Exposure to stressful or traumatic events is associated with increased vulnerability to post-traumatic stress disorder (PTSD). This vulnerability may be partly mediated by effects of stress on the prefrontal cortex (PFC) and associated circuitry. The PFC mediates critical cognitive functions, including cognitive flexibility, which reflects an organism's ability to adaptively alter behavior in light of changing contingencies. Prior work suggests that chronic or acute stress exerts complex effects on different forms of cognitive flexibility, via actions on the PFC. Similarly, PFC dysfunction is reported in PTSD, as are executive function deficits. Animal models that permit study of the effects of stress/trauma on cognitive flexibility may be useful in illuminating ways in which stress-linked cognitive changes contribute to PTSD. Here, we examined the behavioral effects of a rodent model of PTSD – single prolonged stress (SPS) – on performance of two forms of cognitive flexibility: reversal learning and strategy set-shifting. SPS did not impair acquisition of either a response or visual-cue discrimination but did cause slight impairments in the retrieval of the visual-cue rule. During response discrimination reversal, SPS rats made more perseverative errors. In comparison, during set-shifting from the visual-cue to response discrimination, SPS rats did not show enhanced perseveration, but did display increased never-reinforced errors, indicative of impairment in selecting a novel strategy. These data demonstrate that SPS leads to a complex and intriguing pattern of deficits in flexible responding and suggest that impairments in executive functioning associated with PTSD could, in part, be a neuro-cognitive consequence of trauma exposure.

Abbreviations: PTSD, post-traumatic stress disorder; PFC, prefrontal cortex; OFC, orbitofrontal cortex; mPFC, medial prefrontal cortex; SPS, single prolonged stress; FR, fixed ratio; 5-HT, serotonin; MD, mediodorsal thalamic nuclei; NAc, nucleus accumbens; GR, glucocorticoid receptor; WCST, wisconsin card sorting task.

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1. Introduction

Exposure to stressful life events is associated with increased vulnerability to a number of psychiatric disorders, such as mood and anxiety disorders, and notably including post-traumatic stress disorder (PTSD), which is a direct consequence of stress exposure [1–3]. It is well established that stress also affects the functioning of the prefrontal cortex (PFC) [4,5] and accordingly, frontal cortical dysfunctions (mostly indicating hypoactivity) are repeatedly reported in patients with stress-related psychopathologies [6–8].

An important category of cognitive processes that are mediated by the PFC are executive functions, which include complex response pattern planning, working memory and cognitive flexibility [9,10]. Cognitive flexibility involves the updating and modifying of previously learned behavioral response strategies and is critical for successful adaptation to a changing environment [11,12]. Deficits in executive functions are reported in patients with stress-related psychiatric disorders, but it is not clear whether these involve all categories of executive function, and whether such deficits precede or are a consequence of trauma exposure. Preclinical studies using animal models have usefully investigated the impact of stress on working memory [13–15], but relatively few have examined its effect on cognitive flexibility. Those studies that have been conducted have focused largely on two forms of flexibility, reversal learning and set-shifting.

Reversal learning involves acquisition of a response to a previously unreinforced stimulus and simultaneous inhibition of a previously reinforced response, using stimuli that employ a single category or 'dimension' to convey the pertinent information to the animal. For example, in a response discrimination task, the reversal involves switching from a left lever press to a right lever press, but the relevant dimension (in this case, location) remains constant. Set-shifting is a more complex form of flexibility [16,17] that requires an animal to reorganize behavior and employ a new rule, strategy or attentional set. For example, during strategy set-shifting, a cue light may initially inform an animal of which of two levers will be rewarded if pressed, but following the set-shift the animal must instead identify the rewarded lever by its location (left or right lever press) and ignore the cue lights. These two forms of flexibility rely in a dissociable manner on different regions of the PFC – the orbitofrontal cortex (OFC) and medial prefrontal cortex (mPFC) respectively [17–21]. Functional impairment in both set-shifting and reversal learning, and their respective associated regions of the PFC (OFC and mPFC) are implicated in psychiatric symptoms [22].

Exposure to stressful events is a well-established risk factor for the development of a variety of psychiatric disorders [e.g. 1, 2, 23, 24]. Accordingly, there has been considerable research investigating the effects of repeated or "chronic" stress on reversal learning and set-shifting. Chronic stress, modeled in a variety of rodent paradigms, has been shown to impair set-shifting [25–28]. Chronic stress effects on reversal learning are less clear, with reports of no effect [27], inconsistent impairment [26] or marked disruption [29,30], and even one report of facilitation [31]. Studies of acute stress reveal further complexity depending on the nature and context of the stressor, with some studies reporting stress-induced impairments in strategy set-shifting but no effect on reversal learning [32], and others reporting stress-induced facilitation of reversal with no effects on set-shifting [33]. Effects on cognitive flexibility of the types of "traumatic" stress that can lead to a PTSD-like picture have not been studied.

Given the relevance of stress to the development of psychiatric disorders and the potential impact of impaired cognitive flexibility on successful functioning, clarifying the relationship between specific types of stressors and cognitive impairment using disorder-specific animal models may provide important insights into the mechanisms of executive dysfunction in stress-related disorders. Here we examined the impact of a validated rodent model of PTSD – single prolonged stress (SPS) – that produces behavioral and physiological characteristics of PTSD [34–36] on reversal learning and set-shifting.

2. Materials and methods

2.1. Animals

Eighty male Sprague Dawley rats (weighing 150–175 g on arrival) were purchased from Charles River (Portage, MI, USA) for two experiments. They were singly housed at the Veterinary Medical Unit of the Ann Arbor Veterans Affairs Medical Center and maintained on a 12:12 h light/dark cycle with *ad libitum* access to water. Animals were allowed to acclimatize to the colony room for 3 days prior to beginning any experimental procedure. Each rat received approximately 16 g of standard laboratory chow per day to maintain them at ~85% of their free feeding weight. All procedures were approved by the Ann Arbor Veteran Affairs Institutional Animal Care Usage Committee and were in accordance with the National Institute of Health standard for the treatment of animals. At the end of training, all rats were euthanized in a carbon dioxide euthanasia chamber.

2.2. Apparatus

The behavioral apparatus consisted of eight operant boxes (Med Associates, VT, USA). Each box was housed in an individual chamber and was fitted with two Med Associates levers situated on either side of a central magazine. The magazine was supplied by a pellet dispenser system (Med Associates), which delivered 45 mg food pellets (Dustless precision pellets, Bio-serv, NJ, USA). A house light located above the central magazine illuminated each chamber, and cue lights were located above each lever. Boxes were connected to Med Associates interfaces and a PC running MedPC software that controlled experimental contingencies and collected output data.

2.3. Pre-training and SPS

All rats received pre-training, adapted from Floresco et al. [21] and Enomoto et al. [37], to facilitate lever pressing responses; following one week of food restriction, they received ~20 food reward pellets (Bio-serv) in their home cages and the following day began training on the lever press response. On day 1 of lever training, each rat was placed in an operant chamber where ~2 reward pellets, crushed into a fine powder, were placed on an extended lever. They were then rewarded on a fixed ratio-1 (FR-1) for pressing one of the levers (counterbalanced left/right). After a rat reached criterion performance (>50 lever presses during a 30 min session), it was placed back in its home cage. If a rat did not reach the criterion on day 1, it received an additional training session the following day. After criterion was reached on one lever, rats received identical training on the opposite lever until the same criterion was reached.

Following this, rats were trained to press retractable levers. These sessions consisted of 90 training trials and began with the levers retracted and the chamber in darkness. Each trial occurred on a 20 s inter-trial interval and began with illumination of the house light and insertions of one of the two levers into the chamber. If the rat failed to press the lever within 10 s, the lever was retracted, the chamber darkened and the trial was scored as an omission. If the rat responded within 10 s, the lever was retracted, a single pellet was delivered immediately and the house light remained illuminated for another 4 s. In every pair of trials, the left or right lever