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EFFECTS OF STRESS ON BEHAVIORAL FLEXIBILITY IN RODENTS

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Abstract—Cognitive flexibility is the ability to switch between different rules or concepts and behavioral flexibility is the overt physical manifestation of these shifts. Behavioral flexibility is essential for adaptive responses and commonly measured by reversal learning and set-shifting performance in rodents. Both tasks have demonstrated vulnerability to stress with effects dependent upon stressor type and number of repetitions. This review compares the effects of stress on reversal learning and set-shifting to provide insight into the differential effect of stress on cognition. Acute and short-term repetition of stress appears to facilitate reversal learning whereas the longer term repetition of stress impairs reversal learning. Stress facilitated intradimensional set-shifting within a single, short-term stress protocol but otherwise generally impaired set-shifting performance in acute and repeated stress paradigms. Chronic unpredictable stress impairs reversal learning and set-shifting whereas repeated cold intermittent stress selectively impairs reversal learning and has no effect on set-shifting. In considering the mechanisms underlying the effects of stress on behavioral flexibility, pharmacological manipulations performed in conjunction with stress are also reviewed. Blocking corticosterone receptors does not affect the facilitation of reversal learning following acute stress but the prevention of corticosterone synthesis rescues repeated stress-induced set-shifting impairment. Enhancing post-synaptic norepinephrine function, serotonin availability, and dopamine receptor activation rescues and/or prevents behavioral flexibility performance following stress. While this review highlights a lack of a standardization of stress paradigms, some consistent effects are apparent. Future studies are necessary to specify the mechanisms underlying the stress-induced impairments of behavioral flexibility, which will aid in alleviating these symptoms in patients with some psychiatric disorders.

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Key words: reversal learning, set-shifting, norepinephrine, serotonin, attentional set-shifting task, strategy.

INTRODUCTION

Cognitive flexibility, an executive function that enables behavioral changes in response to new environmental demands, is impaired in a variety of psychiatric conditions (Nikiforuk and Popik, 2013; Remijnse et al., 2013; Aloi et al., 2015; Fineberg et al., 2015; Rabinovici et al., 2015; Van Eylen et al., 2015). In order for cognitive flexibility to be adaptive, various mental processes must be coordinated including the inhibition of previously relevant responses, attention, and working memory (reviewed in Dajani and Uddin, 2015). While 'cognitive flexibility' defines the covert mental processes that occur, 'behavioral flexibility' is the overt manifestation of these processes amenable to observation in animal studies (Brown and Tait, 2014). For this reason, the term behavioral flexibility is used to describe the findings of studies contained within this review. In rodents, several tasks of behavioral flexibility have been developed that engage cortical regions analogous to those utilized by humans (Kesner and Churchwell, 2011). Stress has complex effects on behavioral flexibility and the current review aims to synthesize the literature relating to these effects. As the effects of stress on cognition depend upon the type, intensity, and number of repetitions of the stressor (Diamond et al., 2007; Cazakoff et al., 2010; Danet et al., 2010; Nava et al., 2015), we will directly compare the effects of acute (1 day) and a range of repeated stress paradigms (3–35 days) on performance of set-shifting and reversal learning tasks in rodents. Further, the different neurochemical mechanisms mediating these stress effects are discussed where data are available.

Cognitive and behavioral flexibility

Human cognitive flexibility is commonly studied using the intra-dimensional (ID)/extra-dimensional (ED) Set-Shifting Task and the Wisconsin Card Sorting Task (Butler et al., 1991; Odlaug et al., 2010). The study of rodent flexibility is conducted using analogs of these tasks such as the attentional set-shifting task (ASST) and the Operant-based Strategy Set-Shifting Task (OSST) (Fig. 1) (Birrell and Brown, 2000; Floresco et al., 2008). The neural circuits involved in the tasks are conserved among species suggesting the high translational capacity and validity of the rodent tasks (Brady and Floresco, 2015; Durstewitz et al., 2010; Hamilton and Brigman, 2015; Heisler et al., 2015; Izquierdo et al., 2017). In the

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Abbreviations: 5-HT, serotonin; ASST, attentional set-shifting task; CRF, corticotrophin-releasing factor; ED, extra-dimensional; GRs, glucocorticoid receptors; HPA, hypothalamic–pituitary–adrenal; ID, intra-dimensional; mPFC, medial prefrontal cortex; MRs, mineralocorticoid receptors; NE, norepinephrine; NMDA, N-methyl-D-aspartate; OFC, orbitofrontal cortex; OSST, Operant-based Strategy Set-Shifting Task; SNS, sympathetic nervous system.

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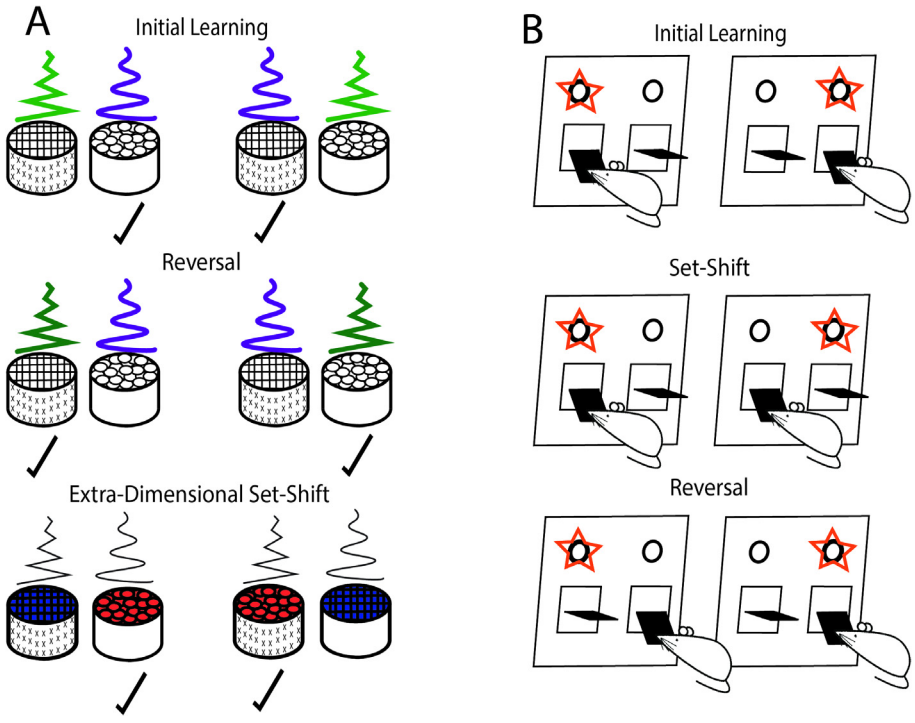

Fig. 1. Rodent behavioral flexibility tasks. (A) Schematic representation of the attentional set-shifting task. The checkmark indicates the rewarded bowl. During initial and reversal learning in this example, the relevant perceptual dimension is scent. An intradimensional set-shift can be conducted with the same stimuli (see text). During extra-dimensional (ED) set-shifting, the relevant dimension becomes the digging medium. (B) Illustration of the operant set-shifting task. The lever near the rat is the correct response. During initial learning the rat must attend to the visual light cue but, following the set-shift and subsequent reversal, the rat must attend to spatial cues to receive food reward.

rodent ASST and OSST, behavioral flexibility is measured using two distinct procedures known as reversal learning and set-shifting. Acquisition of both procedures requires the inhibition of a previously rewarded response rule and its replacement with a new, formerly irrelevant response rule. However, the two procedures differ in the shift of relevant dimension between the old stimulus–response pair and the new one. During reversal learning, the opposite and previously irrelevant response within a stimulus-reward pairing is rewarded (Cools et al., 2002). In contrast, set-shifting requires a new strategy involving a stimulus-reward pairing that was previously in an irrelevant domain (ED shift) or absent from prior trials (ID shift) (Birrell and Brown, 2000; Floresco et al., 2008).

In the ASST (Fig. 1A), rodents use perceptual cues to select and dig in one of two available bowls with the goal of obtaining a food reward (Birrell and Brown, 2000). The stimuli vary on three perceptual dimensions: the bowl and rim texture, the digging medium, and the scent of the digging medium. During reversal learning, all three dimensions remain constant but the previously unrewarded stimulus within the previously learned stimulus–reward pair is rewarded. As an example, during initial learning a rodent could be rewarded for digging in a dill-scented bowl and ignoring a lavender-scented bowl. During subsequent reversal learning (denoted R1), a rodent is then required to dig in the lavender-scented bowl and is not rewarded for exploring the dill scented one. The other procedure used to evaluate behavioral flexibility is set-shifting. An ID set-shift occurs when old exemplars are replaced with novel ones and the new rule remains within the same perceptual dimension as the previous one. ED set-shifting requires a rodent to redirect its attention to a previously ignored perceptual dimension. To continue the earlier example, an ID set-shift would begin with the removal of dill and lavender and their replacement with cinnamon and basil. A rodent would then have to learn that only one bowl (e.g., cinnamon) was rewarded. An ED set-shift would take place if a rodent was required to ignore scent and constantly select the bowl containing a given digging medium (e.g., rice and not woodchips), regardless of its scent. Reversal learning within the ASST is not limited to a single phase of the task and can also be tested following an ID set-shift (R2), and after an ED set-shift (R3).

The other commonly used task to measure rodent flexibility is the OSST (Fig. 1B). This task is conducted within an operant conditioning chamber containing two response levers and a stimulus light above each (Brady and Floresco, 2015). During the initial learning phase, a rodent must learn a light-based rule and press the lever below the lit light to obtain a food reward. During set-shifting a rodent is required to disregard the light and adopt a spatial strategy such that it consistently responds to one lever (e.g., left). Note that measurements of ID set-shifts are not possible within the OSST. Finally, the reversal learning phase rewards a rodent for pressing the opposite lever (e.g., right). Recently, a new task has combined the three perceptual domains of the ASST with the operant style of the OSST in an intra-/extra-dimensional

"operon" task (Scheggia and Papaleo, 2016). The effects of stress on this task have yet to be reported so it will not be discussed further. Trials to criterion and total errors are used in both the ASST and OSST as measures of flexibility. Total errors can be analyzed further by subtype (Floresco et al., 2009). Perseveration reflects an inability to disengage from the previous rule while regressive errors occur when the subject inconsistently responds using the new rule once perseveration has ceased (Floresco et al., 2009; Nilsson et al., 2015). An increase in regressive errors may be indicative of impairments in more general cognitive abilities, such as attention. Never reinforced errors occur when a rodent makes a response not previously or currently rewarded on the task.

Distributed cortico-striatal-limbic circuits mediate behavioral flexibility and several reviews have described these neuronal pathways (Floresco et al., 2009; Kehagia et al., 2010; Bissonette et al., 2013; Hamilton and Brigman, 2015). Experiments assessing the effects of stress on behavioral flexibility have primarily focused on the prefrontal cortex (PFC), thus we will highlight the dissociable involvement of different sub-regions of PFC in reversal learning and set-shifting (Fig. 2). The orbitofrontal cortex (OFC) is necessary for reversal learning in a variety of species including humans, non-human primates, rats, and mice (Hornak et al., 2004; Izquierdo et al., 2004; Bissonette et al., 2008). Lesions of the OFC selectively impair reversal learning (McAlonan and Brown, 2003; Schoenbaum, 2003; Boulougouris et al., 2007), while sparing set-shifting (McAlonan and Brown, 2003; Ghods-Sharifi et al., 2008). The precise role of the OFC in reversal learning is inconsistently described throughout the literature (Stalnaker et al., 2015). Initially, it was believed to play a primary role in response inhibition and the suppression of inappropriate behavior. Functional neuroimaging studies have shown enhanced activation of the OFC following successful inhibitions in the Go/NoGo impulsivity task (Horn et al., 2003). Additionally, functional and anatomical changes in the OFC are observed in obsessive compulsive disorder, a psychiatric illness characterized by impaired behavioral suppression (Atmaca et al., 2007; Hou et al., 2012; Zhang et al., 2015). However, lesions of the OFC do not consistently impair response inhibition in all behavioral paradigms (Chudasama et al., 2006; Rudebeck et al., 2013). Single-unit recordings suggest the OFC may be required for response planning when selecting between perceptually similar actions (Bryden and Roesch, 2015). Other studies suggest a critical role of the OFC is prediction and evaluation of behavioral outcomes but this is inconsistently supported (Moorman and Aston-Jones, 2014; Rudebeck and Murray, 2014; Stalnaker et al., 2015). Regardless of its precise role in the cognitive aspects of behavioral flexibility, the OFC is undoubtedly important in reversal learning (Izquierdo et al., 2017) but not necessarily set-shifting.

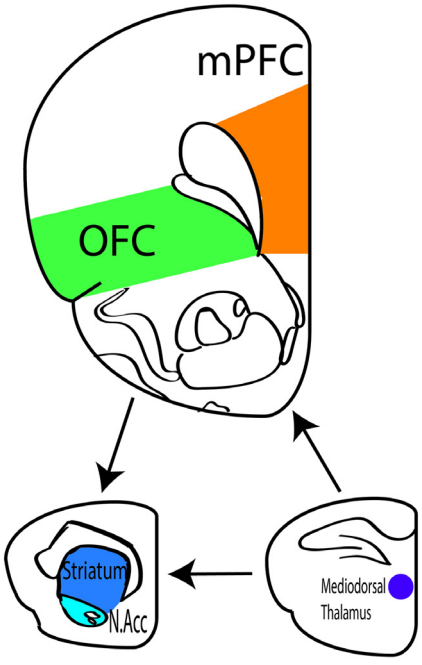

Fig. 2. Simplified diagram depicting the cortical regions involved in behavioral flexibility. Key regions of interest located within the prefrontal cortex include the orbitofrontal cortex (OFC) and the medial prefrontal cortex (mPFC). Regions outside the prefrontal cortex include the striatum, nucleus accumbens (N. Acc), and the mediodorsal thalamus. Arrows depict the neuronal connections between regions.

The medial prefrontal cortex (mPFC) is necessary for set-shifting in the ASST (Birrell and Brown, 2000) and OSST (Floresco et al., 2008). The specificity of the mPFC for set-shifting has been demonstrated using pharmacological and anatomical manipulations. Bilateral injections of ibotenic acid and ischemic lesions of the mPFC impair ED set-shifting but have no effect on reversal learning (Birrell and Brown, 2000; Déziel et al., 2015). Similarly, local infusion of anesthetic increases trials to criterion and overall errors in set-shifting but spares reversal learning and visual cue discriminations (Ragozzino et al., 1999; Floresco et al., 2008). GABAergic interneurons within the mPFC are also implicated in set-shifting. Mice with abnormal GABAergic fast-spiking interneuron development have behavioral flexibility impairments that are reversed with optogenetic stimulation of these neurons at gamma frequencies (Cho et al., 2015). Similarly, in some developmental rodent models of schizophrenia, the normal maturation of the mPFC is disrupted and set-shifting impairments but not consistent changes in reversal learning are observed (Zhang et al., 2012; Placek et al., 2013; Ballendine et al., 2015). The role of the mPFC in behavioral flexibility may stem from its involvement in rule learning and the regulation of goal-directed behavior (Balleine and O'Doherty, 2010; Durstewitz et al., 2010). Neuronal encoding within the mPFC is rule-specific, with different neuron populations representing distinct rules and categories (Durstewitz et al., 2010; Roy et al. 2010; Bissonette and Roesch, 2015). Further, this area may be crucial for linking contexts and reward outcomes (Euston et al., 2012).

Stress and the neural circuitry related to flexibility

Allostasis is the term used to describe the body's effort to return to a balanced state following a disturbance in homeostasis, such as occurs during a stressful event.

This process also increases an organism's likelihood of survival by heightening arousal and enhancing memory (Roozendaal, 2000). Allostasis is primarily due to the activation of two complementary systems: the sympathetic nervous system (SNS) and the hypothalamic–pituitary–adrenal (HPA) axis (McEwen and Wingfield, 2003). Seconds following exposure to stress, the SNS is activated and catecholamines, primarily epinephrine and norepinephrine (NE), are released. These hormones enhance physiological arousal in the peripheral nervous system, a state commonly referred to as the "fight or flight" response. The HPA axis response is subsequently initiated and begins with the secretion of corticotrophin-releasing factor (CRF) from the paraventricular nucleus within the hypothalamus. CRF stimulates the release of adrenocorticotrophic hormone (ACTH) from the anterior pituitary gland, which ultimately leads to cortisol/corticosterone secretion from the adrenal glands. Activation of the HPA axis is tightly regulated through the negative feedback of glucocorticoids. The liposolubility of glucocorticoids allows them to diffuse across the blood brain barrier, accounting for some of cognitive changes following stress (Kim and Diamond, 2002; Lupien et al., 2007; Howland and Wang, 2008; Cazakoff et al., 2010; Nikiforuk and Popik, 2011; Schwabe et al., 2012). Glucocorticoid (GR) and mineralocorticoid (MR) receptors are the known receptor subtypes for corticosterone. These two receptors are distinguished several ways including their distribution within the cortex, affinity for corticosterone, and role in cognition. GR are globally distributed throughout the brain whereas MR are highly expressed within the limbic system. MR have ten times greater affinity for corticosterone than GR, which may relate to their roles in optimal memory performance (de Kloet et al., 2005; Lupien et al., 2007; Vogel et al., 2016). During allostasis, the release and return to baseline of glucocorticoids is slower than catecholamines (Sapolsky et al., 2000; Lupien et al., 2007; Papadopoulou et al., 2015). However, the HPA axis works in parallel with the SNS and the activation of one results in enhanced activation of the other (Itoi et al., 1994; Flak et al., 2014).

Unlike the acute response, prolonged stress exposure exhausts homeostatic maintenance mechanisms and produces psychological, physiological, anatomical and cognitive changes (Goldstein and McEwen, 2002; Anisman and Matheson, 2005; McEwen et al., 2015). Within the psychological realm, severe and prolonged stressful life events increase the risk of diagnosis of major depression (Kendler et al., 1999). Individuals with depression and post-traumatic stress disorder have elevated levels of glucocorticoids, which are associated with hippocampal atrophy and memory impairments (Sapolsky, 2000; Kvarta et al., 2015). These relationships have been studied using animals where subjecting rodents to various stress paradigms causes symptoms similar to depression and post-traumatic stress disorder (Darcet et al., 2014; Burgdorf et al., 2015). Physiological changes that follow repeated stress include immunosuppression, increased risk of dyslipidemia and hypertension, and diminished glucose tolerance (An et al., 2015; Razzoli et al., 2015; Xiang et al., 2015). The influence of repeated stress on anatomy is reflected in region-dependent alterations of GR abundance throughout the cortex. Down-regulation of GR has been observed within the prefrontal cortex (Mizoguchi et al., 2003). In the hippocampus, some studies report an up-regulation (Mizoguchi et al., 2003), others observe sex-specific variations (Kitraki et al., 2004; Wright et al., 2006), and the remaining show no shifts in GR at all (Herman and Spencer, 1998; Romeo et al., 2008). Alterations in dendritic morphology throughout the cortex are also observed with repeated stress exposure. Repeated restraint stress induces the retraction of apical dendrites and the atrophy of distal branches within mPFC pyramidal neurons (Liston et al., 2006; Dias-Ferreira et al., 2009). These changes in mPFC dendritic morphology are similar whether the animal experienced daily stress or corticosterone treatment, suggesting that HPA axis activation is sufficient to produce these anatomical changes (Cook and Wellman, 2004; Brown, 2005). Other regions within the PFC, including the prelimbic and infralimbic cortex, show dendritic atrophy following chronic stress (Eiland et al., 2012; Goldwater et al., 2009). In contrast, the OFC shows increased apical dendritic arborization following repeated restraint stress (Liston et al., 2006) and lengthened dendrites are observed in the amygdala and striatum (Dias-Ferreira et al., 2009; Eiland et al., 2012).

Stress produces a heterogeneous array of changes in cognition (Kim and Diamond, 2002; Lupien et al., 2007; Howland and Wang, 2008; Cazakoff et al., 2010; Nikiforuk and Popik, 2011; Schwabe et al., 2012; Cozzoli et al., 2014). Some of the cognitive functions altered by stress and related to cognitive flexibility include working memory, attention, and reward processing (Arnsten, 2009; Holmes and Wellman, 2009; Arnsten, 2015). Further, the strategy used to make decisions following stress may be biased away from goal-oriented behavior and toward a more habitual response (Dias-Ferreira et al., 2009). These changes are influenced by factors related to the stress paradigm and the subject exposed to stress. Short-term GR-mediated actions as well as the long-term genomic changes result from corticosterone binding to its receptors. Stressors may also differ by type and length of application, both of which influence the magnitude of corticosterone elevation and corresponding task performance (Koolhaas et al., 2011; Lee et al., 2013; Smitha and Mukkadan, 2014).

Due to the variety of stressors, subjects, and behavioral tasks the current literature on stress and cognition is difficult to interpret. The lack of a "stress phenotype" is perpetuated by the inconsistent use of a stressor type, duration and repetition, each uniquely influencing corticosterone levels (Koolhaas et al., 2011; Romero et al., 2015). Further, the reliance on glucocorticoids in diagnosing stress may be inappropriate as HPA axis activation follows social and sexual behavior as well (Woodson, 2003; Romero et al., 2015). Regardless, corticosterone remains the standard method to objectively measure stress in rodents (Dickens and Romero, 2013). With the range of stress paradigms, measurements, subjects, and variables, a universal stress phenotype may be unrealistic (Weaver et al., 2004; Smitha and Mukkadan,

2014; Romero et al., 2015). Instead, there may be more to gain by modifying the behavioral definition of stress to include several categories, each limited to a specific cognitive paradigm. Therefore, it is the aim of this review to provide a comprehensive analysis of the influence of stress on rodent behavioral flexibility by detailing the existing literature. In order to achieve this, reversal learning and set-shifting are discussed independently and the stressor duration, type, and days of repetition as well as specific task, rodent strain and the subject's sex are detailed in the accompanying figures and tables.

Stress and behavioral flexibility in rodent models

The reviewed literature was obtained from the PubMed database using combinations of the search terms 'cognitive flexibility', 'set-shifting', 'reversal learning', 'acute stress', 'chronic stress', and 'repeated stress'. All collected papers were published in English, used adult rodent subjects, and included a behavioral stressor. The references cited within these papers provided additional resources. Twenty-five papers were selected for inclusion and summarized in Figs. 3 and 4 as well as Tables 1–3. The papers were sorted according to the number of stress exposures, ranging from acute (a single stress session) to repeated (3–35 daily sessions). Among the studies, a total of four flexibility tasks were identified. Following acute stress, behavioral flexibility was most frequently measured using the OSST but following repeated stress the ASST was more commonly used. Twenty-four of the 25 papers used exclusively male subjects, which precluded an assessment of potential sex differences in the effects of stress on flexibility. It is important to note that, due to the variety of stressors, stress application lengths, stress exposures, and behavioral paradigms, the broad generalizability of this summary may be limited. Corticosterone release follows a circadian rhythm and the time of day that a rodent is stressed may contribute to the amplitude of corticosterone released (Ishikawa et al., 1995; Kalsbeek et al., 2012). The influence of time-of-day could not be addressed as the majority of experiments occurred during the light cycle. Additionally, the studies do not directly address how prior learning of the task may have affected performance. For example, the OSST typically spans several days, with reversal learning and set-shifting occurring on separate days. Thus, rodents can be stressed immediately prior to each flexibility measure. In contrast, set-shifting and reversal learning are typically assessed in the ASST during a single day. Within the limits, patterns among the published studies will be subsequently identified and discussed.

Acute stress

Four studies examined behavioral flexibility following acute stress (Table 1). Reversal learning was facilitated by restraint and elevated platform stress (Dong et al., 2013; Thai et al., 2013) but was unaffected by an in-context acute tail pinch (Butts et al., 2013). In contrast, acute tail pinch stress prior to OSST set-shifting led to impairment (Butts et al., 2013) but restraint had no effect on set-shifting (Thai et al., 2013). A single prolonged stressor 10 days prior to testing altered set-shifting performance by subtly increasing never-reinforced errors but reducing perseverative errors. Following the single prolonged stressor, perseverative errors were reported to decrease in set-shifting but increase in reversal learning (George et al., 2015). This suggests that the stressed rats were readily able to disengage from unrewarded strategies in a currently irrelevant perceptual dimension but struggled to switch between targets within the same perceptual domain. Thus, this prolonged stressor may have dissociable effects on the OFC and mPFC. These effects could also be the result of an altered mediodorsal-thalamic nucleus and nucleus accumbens connection as this connection is important for facilitating set-shifting strategies (Block et al., 2007). Reversal learning may also be more sensitive to the heightened glucocorticoid receptor (GR) expression caused by this stress paradigm (Knox et al., 2012).

The inconsistent effects of the different acute stress paradigms on behavioral flexibility may be interpreted in a variety of ways; however, firm conclusions are difficult given the limited number of studies. None of the stress paradigms were replicated among the acute stress studies. The stressors ranged from a single restraint session (Thai et al., 2013) to a single prolonged stress consisting of three unique stressors applied sequentially (George et al., 2015). Although this variety prevents the assessment of other variables such as stressor application length, comparison of the studies suggests a trend relating stressor severity to flexibility. Stressor severity is often interpreted by accounting for its perceived predictability and controllability (Koolhaas et al., 2011). Specific to the studies mentioned, restraint stress is relatively mild due to its consistency during administration (Plumb et al., 2015), and is sharply contrasted by high unpredictability and uncontrollability of the varying length and stressor types administered during the single prolonged stress session (George et al., 2015). Thus, the single prolonged stressor was likely the most severe and this may partially explain the impairments observed in set-shifting and reversal learning. The inconsistent findings may also be due to the context in which the stress was presented. For example, whether the stress was applied in the same context (i.e., operant conditioning chamber – Butts et al., 2013) or a novel room (Thai et al., 2013) may have contributed to the different effects observed among the studies of reversal learning and set-shifting. The differences in performance may also be explained by the intrinsic differences in difficulty between set-shifting and reversal learning. Of the two tasks, set-shifting is believed to be more cognitively challenging, although the measure of trials to criterion does not always support this assertion within the OSST (Nilsson et al., 2015). Finally, the different stress effects may be accounted for in the time between the stressor application and flexibility task. This idea was briefly explored by Butts and colleagues (2013), who found that acute tail pinch stress only impaired set-shifting when it occurred 15 min, and not 24 h, prior to task completion. However, the same time delays had no effect on reversal learning.

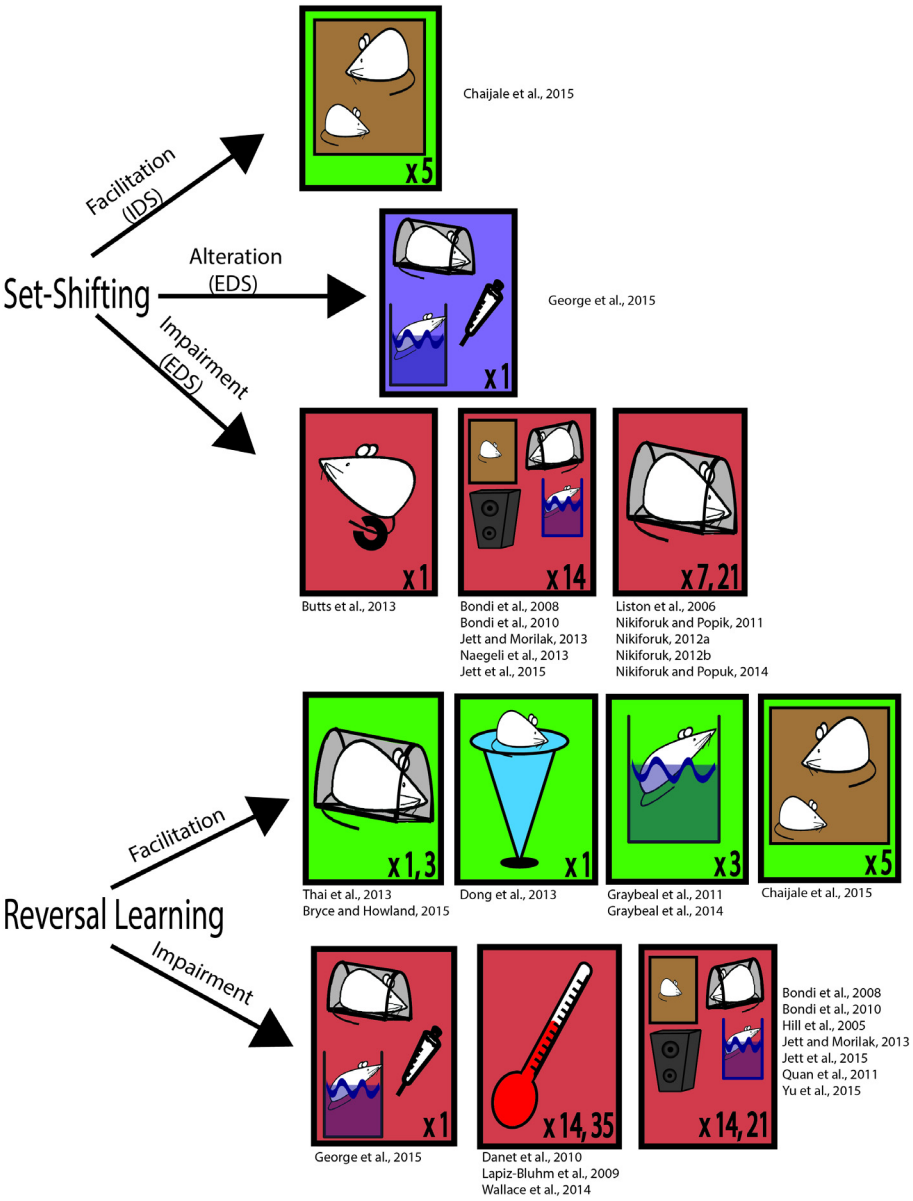

Fig. 3. Visual representation of the effects of different stress paradigms on set-shifting and reversal learning. The number of stress sessions is indicated by the number within each box. Note that George et al. (2015) used induction with gas anesthesia as the final component of the stressor in their study; this component is depicted with a syringe for simplicity.

Thai and colleagues (2013) found that restraint stress immediately followed by reversal learning in the OSST improved reversal learning but had no effect on set-shifting.

Repeated stress (3–7 sessions)

Of the studies using three repeated stress sessions, none measured set-shifting and all found facilitated reversal learning in a task employing touchscreen-equipped operant conditioning chambers (Table 2). C57BL/6J mice and Long Evans rats demonstrated enhanced reversal learning following three days of swim stress or restraint stress respectively (Graybeal et al., 2011; Graybeal et al., 2014; Bryce and Howland, 2015). Interestingly, this change was specific to late reversal learning in two of the studies (Graybeal et al., 2011; Bryce and Howland, 2015), which is noteworthy given that this reversal learning task requires several days to complete. The facilitation is similar to the findings of single session restraint stress (Thai et al., 2013), suggesting that three days of stress may not be enough for the detrimental behavioral changes seen following longer repeated stress protocols to be observed (see Repeated stress (more than 7 sessions) section). Strain differences in flexibility following stress were observed by Graybeal et al. (2014), as DBA/3J mice experience no change in reversal learning after the identical stress paradigm as C57BL/6J mice. These differences may be accounted for by strain variations in behavioral stress responses and neurochemical activity (D'Este et al., 2007; Millstein and Holmes, 2007).

Table 1. Effects of acute stress on behavioral flexibility. The duration of stress is indicated within the stressor column. Effects on reversal learning and set-shifting are shown in separate columns. Behavioral flexibility performance is relative to that of control rats. Only statistically significant findings are reported. MWM, Morris Water Maze; OSST, Operant-based Strategy Set-Shifting Task; SD, Sprague Dawley; TTC, trials to criterion

Stressor (duration)	Stress timeline	Task	Reversal learning performance	Set-shifting performance	Strain/ species	Reference
In-context tail pinch (15 min)	Prior to set-shifting or reversal learning	OSST	No effect	Impairment; ↑ TTC ↑ Perseverative errors	Male SD/ rat	Butts et al. (2013)
Elevated platform (30 min)	Prior to reversal training	MWM	Improvement; ↓ Escape latency during early trials ↑ Time in correct quadrant	Not tested	Male SD/ rat	Dong et al. (2013)
Restraint (30 min)	Prior to set-shifting or reversal learning	OSST	Improvement; ↓ TTC ↓ Total errors	No effect	Male SD/ rat	Thai et al. (2013)
Single prolonged stress (2.5 h)*	7 days prior to lever retraining	OSST	Impairment; ↑ Perseverative errors	Altered; ↑ Never-reinforced errors ↓ Perseverative errors	Male SD/ rat	George et al. (2015)

* Consisted of restraint (2 h), forced swim (20 min), and ether exposure (anesthesia induction).

Five days of resident intruder stress significantly reduced perseverative errors in reversal learning and trials to criterion in ID set-shifting during the ASST (Chaijale et al., 2015). Of all twenty-five studies reviewed, this study is unique in that it reports stress-induced facilitation of both reversal learning and any type of set-shifting. Unfortunately, it is difficult to infer why this may be as it is the only study using resident intruder stress in male rats. Another study using the same stress paradigm with the OSST in female rats found no effect on set-shifting and a selective reversal learning impairment in rats who quickly expressed defeat (Snyder et al., 2015a). As previously mentioned, ID set-shifting cannot be measured with the OSST, thus this measure of behavioral flexibility could not be tested. These sex-specific effects in a female cohort suggests sex differences may exist for the effects of stress on behavioral flexibility, although considerably more research will be required to confirm this assertion.

None of the studies using seven restraint stress sessions found a change in reversal learning but they did observe increased trials to criterion during ED set-shifts in the ASST (Nikiforuk, 2012a; Nikiforuk 2012b; Nikiforuk and Popik, 2014). These results contrast the findings from fewer stress sessions showing restraint stress accelerates reversal learning (Thai et al., 2013; Graybeal et al., 2014; Bryce and Howland, 2015). This suggests that, at some point between four to seven days of stress repetition, the effects of restraint on reversal learning shift from beneficial to non-influential. The influence of a stressor on flexibility depends upon the number and length of sessions, which ultimately produces varying physiological responses related to the duration of HPA axis activation (Buynitsky and Mostofsky, 2009). For example, one study found that seven days of restraint stress in rhesus monkeys reduced cortisol secretion following the stressor, which suggests that the lack of improvement in reversal learning following 7 days of reversal stress may be due to altered glucocorticoid levels (Ruys et al., 2004). However, another explanation for this change is the increased length of stressor sessions from 30 min (Bryce and Howland, 2015) to 1 h (Nikiforuk, 2012a). Additionally, the acute and 3-session studies measured flexibility using the touchscreen visual discrimination task and the OSST, whereas the seven session studies used the ASST. Nikiforuk and Popik (2011) explored the long-term consequences of repeated stress by testing flexibility performance 4, 7, 14, and 21 days after the end of the seven restraint sessions. They observed that the impaired acquisition of the ED set-shift occurred irrespective of days post-stress and the level of impairment was also similar. This suggests that 7 days of restraint stress produces long-lasting effects that remain for up to 3 weeks following stress.

Repeated stress (more than seven sessions)

The identified papers with greater than seven stress sessions utilized two different stress paradigms, chronic intermittent cold stress and chronic unpredictable stress (Table 2). Six hours of chronic intermittent cold stress daily for 14 days consistently increased the trials to criterion during reversal learning in the ASST (Bondi et al., 2008; Bondi et al., 2010; Jett and Morilak, 2013; Naegeli et al., 2013; Jett et al., 2015). This stress paradigm generally appears to have no effect on set-shifting with only one of four groups in a single study demonstrating set-shifting impairments (Danet et al., 2010). Impaired set-shifting was also found when the number of stress sessions was increased to 35 (Danet et al., 2010). Overall, it appears as though chronic intermittent cold stress selectively affects reversal learning, perhaps by specifically interacting with OFC function. For example, reduced serotonin (5-HT) levels are found within the OFC following chronic intermittent cold stress (Lapiz-Bluhm et al., 2009).

Table 2. Effects of repeated stress on behavioral flexibility. Studies are categorized according to the number of stress sessions. Behavioral flexibility is broken down according to set-shifting and reversal learning. Task performance is relative to that of control rats. Only statistically significant findings are reported. ASST, attentional set-shifting task; CIC, chronic intermittent cold stress; CUS, chronic unpredictable stress; EDS, extradimensional shift; IDS, intradimensional shift; LC, locus coeruleus; LE, Long Evans; MWM, Morris Water Maze; SD, Sprague Dawley; TTC, trials to criterion; VD, visual discrimination

Stressor (duration)	Stress finish	Task	Reversal learning performance	Set-shifting performance	Strain/ species	Reference
3 days						
Swim stress (10 min)	Prior to reversal	Touchscreen VD task	Improved late reversal; ↓ Errors ↓ Correction trials	Not tested	MaleC57BL/ 6J/mouse	Graybeal et al. (2011)
Swim stress (10 min)	Prior to reversal	Touchscreen VD task	No effect	Not tested	Male DBA/ 2J/mouse	Graybeal et al. (2014)
			Improvement; ↓ Errors ↓ Correction trials ↓ Sessions	Not tested	Male C57BL/ 6J/mouse	
Restraint (30 min)	Once/day prior to reversal learning	Touchscreen VD task	Improved late reversal; ↓ Errors, ↓ Correction trials ↓ Sessions	Not tested	Male LE/rat	Bryce and Howland (2015)
5 days						
Resident intruder stress (45 min)*	2 days prior to training	ASST	Improvement; ↓ Perseverative errors	Improved IDS; ↓ TTC	Male SD/rat	Chaijale et al. (2015)
Resident intruder stress (45 min)*	3 days prior to training	OSST	No effect**	No effect	Female SD/ rat	Snyder et al. (2015a)
7 Days						
Restraint (1 h/day)	4, 7, 14 or 21 days prior to testing	ASST	No effect	Impaired EDS; ↑ TTC (Regardless of stress-test delay)	Male SD/rat	Nikiforuk and Popik (2011)
Restraint (1 h/day)	14 days prior to testing	ASST	No effect	Impaired EDS; ↑ TTC	Male SD/rat	Nikiforuk (2012b)
Restraint (1 h/day)	14 days prior to testing	ASST	No effect	Impaired EDS; ↑ TTC	Male SD/rat	Nikiforuk (2012a)
Restraint (1 h/day)	14 days prior to testing	ASST	No effect	Impaired EDS; ↑ TTC	Male SD/rat	Nikiforuk and Popik (2014)
14 days						
CUS (stressor dependent)	3 days prior to testing	ASST	Impaired R1 and R3; ↑ TTC	Impaired EDS; ↑ TTC	Male SD/rat	Bondi et al. (2008)
CIC (6 h/day)	1 day prior to testing	ASST	Impaired R1; ↑ TTC	No effect	Male SD/rat	Lapiz-Bluhm et al. (2009)
CUS (stressor dependent)	3 days prior to testing	ASST	Impaired R1 and R3; ↑ TTC	Impaired EDS; ↑ TTC	Male SD/rat	Bondi et al. (2010)
			Impaired R1; ↑ TTC	Impaired EDS; ↑ TTC	Male SD/rat	
CIC (6 h/day)	3, 7, 14, 21 days prior to testing	ASST	Impaired R1; ↑ TTC (Only with 3 day stress-test delay)	No effect	Male SD/rat	Danet et al. (2010)
CIC (6 h/day)	3 days prior to testing	ASST	Impaired R1; ↑ TTC	No effect	Male SD/rat	
CUS (stressor dependent)	1 day prior to training	ASST	Impaired R1; ↑ TTC	Impaired EDS; ↑ TTC	Male SD/rat	Jett and Morilak (2013)
CUS (stressor dependent)	1 day prior to testing	ASST	No effect	Impaired EDS; ↑ TTC	Male SD/rat	Naegeli et al. (2013)
CIC (6 h/day)	1 day prior to training	ASST	Impaired; ↑ TTC	Not tested	Male SD/rat	Wallace et al. (2014)
CUS (stressor dependent)	1 day prior to testing	ASST	Impaired R1; ↑ TTC	Impaired EDS; ↑ TTC	Male SD/rat	Jett et al. (2015)

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Table 2 (*continued*)

Stressor (duration)	Stress finish	Task	Reversal learning performance	Set-shifting performance	Strain/ species	Reference
21 days						
CUS (stressor dependent)	1 day prior to reversal	MWM reversal	Impaired; ↑ escape latency ↑ time in previously correct quadrant	Not tested	Male LE/rat	Hill et al. (2005)
Restraint (6 h/day)	1 day prior to testing	ASST	No effect	Impaired EDS; ↑ TTC	Male SD/rat	Liston et al. (2006)
CUS (stressor dependent)	1 day prior to training	MWM reversal	Impairment; ↑ reversal training escape latency ↓ platform crossing ↓ time spent in correct quadrant	Not tested	Male Wistar/ rat	Quan et al. (2011)
CUS (stressor dependent)	1 day prior to training	MWM reversal	Impairment; ↑ reversal training escape latency ↓ platform crossings ↓ time in correct quadrant	Not tested	Male Wistar/ rat	Yu et al. (2015)
35 days						
CIS (6 h/day)	3 days prior to testing	ASST	Impaired R1; ↑ TTC	No effect	Male SD	Danet et al. (2010)

[*] The resident and intruder were allowed to interact until either the intruder exhibited a submissive defeat posture (> 2 s frozen in a supine position) or 15 min elapsed. Upon reaching one of these criteria, the animals were separated by a wire barrier, allowing only auditory, olfactory and visual contacts for the remainder of the 30-min test period.

[**] When performance was subdivided according to stress response, rats who demonstrated defeat quickly after introduction to the intruder had impaired reversal latencies measured by increased trials to criterion.

The second stress paradigm that was repeated for greater than seven days was chronic unpredictable stress. Within this paradigm a variety of stressors are used, including restraint and swim stress as well as food deprivation. Of the studies with more than seven days of chronic unpredictable stress, all but one demonstrated impairments in reversal learning (see Table 2 for specific references). This may be explained by a shift in decision making following this stress paradigm, as previous studies have demonstrated the modification of behavior from rewarded-directed to habitual (Dias-Ferreira et al., 2009). Regardless of the stressor used, the studies demonstrated consistently impaired R1 learning, sometimes impaired R3 and never impaired R2. The differences among reversal learning stages within the ASST may be explained by the pattern of cognition required during each (Danet et al., 2010). During the first reversal, the subject must establish the concept of a reversal rule and then navigate within the stimuli-reward pair, which likely makes the R1 stage particularly vulnerable to manipulations. The second reversal follows an ID set-shift and the previously learned reversal rule can be directly applied as the current stimuli–reward pair is within the same perceptual dimension. The lack of new learning required for this stage may make it stress resistant. Finally, although the third reversal uses the same abstract concept as the first two, it must be applied to a new perceptual dimension. Thus, the likelihood of stress-induced impairments is increased.

The effects of twenty-one days of repeated stress were most frequently assessed using reversal learning within the Morris Water Maze. These studies found impaired reversal learning following chronic unpredictable stress as evidenced by increased escape latencies (Hill et al., 2005; Quan et al., 2011) and time spent in the previously correct quadrant (Yu et al., 2015). Two of the studies also noted stressed rats had decreased mean platform crossings further supporting learning impairments. The deficits observed were the similar regardless of whether Long Evans or Wistar rats were studied. Another study used 21 days of repeated stress and found impaired ED set-shifting but not reversal learning within Sprague–Dawley rats in the ASST (Liston et al., 2006). This finding replicates the cognitive changes seen after 7 days of repeated restraint stress (Nikiforuk, 2012a). As discussed in the previous stress sections, the differences in flexibility changes following 21 days of repeated stress may be due to flexibility task, strain, or the stressor used.

POTENTIAL MECHANISMS

As reviewed, stress has complex and varied effects on reversal learning and set-shifting. A number of studies have used a pharmacological approach to examine the mechanisms mediating these behavioral effects. The final section of the review will detail these findings to provide insight into the specific neurobiological

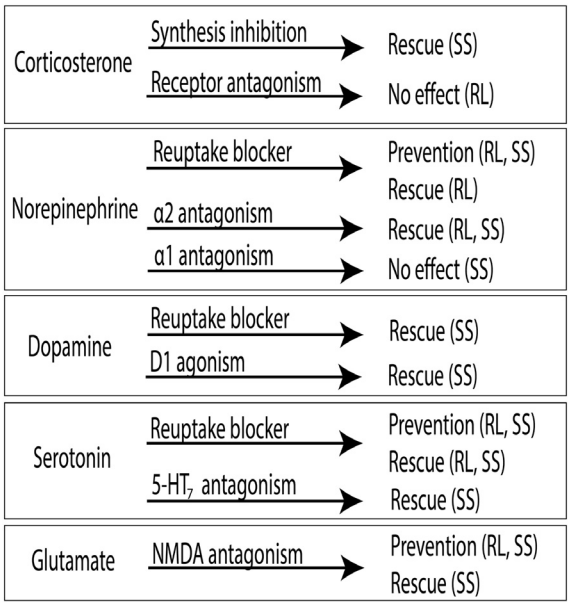

Fig. 4. Simplified presentation of the varying effects of pharmacological manipulations on stress-induced behavioral flexibility changes. The majority of studies investigated the effects of manipulating corticosterone, norepinephrine, dopamine, serotonin, or glutamate availability or their respective receptors.

consequences of stress that underlie the behavioral changes. The blockade of impaired behavioral flexibility resulting from the administration of a pharmacological agent throughout the stressing period is termed "prevention" whereas a change in performance due to acute drug administration prior to testing is termed "rescue". These experiments are summarized in Table 3 and Fig. 4.

CRF and corticosterone

As mentioned, behavioral changes that follow acute and chronic stress are, at least partially, a consequence of HPA axis involvement. For example, CRF promotes corticosterone secretion and is involved in the regulation of neuromodulator systems including 5-HT and NE (Valentino and Van Bockstaele, 2008; Fox and Lowry, 2013). Therefore, some studies have directly injected CRF and observed how it influences other neurotransmitter systems and behavioral flexibility. In one study, CRF (30 ng) infused into the dorsal raphe nucleus reduced 5-HT levels in the mPFC and improved ED set-shifting in the OSST. However, CRF infusions of 10 or 100 ng had no effect when compared to vehicle treatment (Snyder et al., 2015b). Interestingly, when the rats were subjected to five days of restraint stress in the three days prior to

Table 3. Effects of pharmaceutical treatment on behavioral flexibility following stress. Performance changes are relative to performance of stressed vehicle-treated rats. The route of administration is located within the dose column. Treatment is organized according to stress treatment (acute or repeated). BDNF, Brain-Derived Neurotrophic Factor; RL, reversal learning; RT, reversal training; SS, set-shifting; SSRI, selective serotonin reuptake inhibitor

Drug	Mechanism	Dose	Administration	Stressor	Performance change	Reference
Acute stress						
RU38486	GR-selective antagonist	10 mg/kg (i.p.)	Acute, prior to stress	Restraint	No effect (RL)	Thai et al. (2013)
Spironolactone	MR-selective antagonist	50 mg/kg (i.p.)	Acute, prior to stress	Restraint	No effect (RL)	
3 days						
BDNF	Growth factor	0.08 μg (infused vmPFC)	Acute, following final stress session	Swim stress (10 min)	Rescue (RL)	Graybeal et al. (2011)
RU38486	GR-selective antagonist	10 mg/kg (i.p.)	Repeated, prior to each restraint session	Restraint (30 min)	No effect (RL)	Bryce and Howland (2015)
7 days						
Metyrapone	Corticosterone synthesis inhibitor	50 mg/kg (i.p.)	Repeated, prior to each restraint session	Restraint (1 h)	Prevention (SS)	Nikiforuk and Popik (2011)
Nomifensine	Norepinephrine-dopamine reuptake inhibitor	0.3 or 1 mg/kg (i.p.)	Acute, 30 min prior to testing	Restraint (1 h)	Rescue (SS)	
Desipramine	Tricyclic antidepressant	3 or 6 mg/kg (i.p.)	Acute, 30 min prior to testing	Restraint (1 h)	Rescue (SS)	
Fluoxetine	SSRI	1 or 3 mg/kg (i.p.)	Acute, 30 min prior to testing	Restraint (1 h)	Rescue (SS)	
SKF 81297	D1 receptor agonist	0.1 or 0.3 mg/kg (i.p.)	Acute, 30 min prior to discrimination	Restraint (1 h)	Rescue (SS)	Nikiforuk (2012b)
SB-269970	5-HT$_7$ receptor antagonist	0.3 or 1 mg/kg (i.p.)	Acute, 30 min prior to testing	Restraint (1 h)	Rescue (SS)	Nikiforuk (2012a)

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Table 3 (*continued*)

Drug	Mechanism	Dose	Administration	Stressor	Performance change	Reference
Ketamine	Non-competitive NMDA receptor antagonist	10 mg/kg (i.p.)	Repeated, prior to each restraint session	Restraint (1 h)	Prevention (SS)	Nikiforuk and Popik (2014)
14 days						
Milnacipran	Serotonin-norepinephrine reuptake blocker	30 mg/kg/day (i.p. pump)	Chronic, 7 days prior to stress, prior to each stress session and prior to testing	CUS	Prevention/ rescue (SS)	Naegeli et al. (2013)
Desipramine	Tricyclic antidepressant	5 mg/kg/day (i.p. pump)	Chronic, 7 days prior to stress, prior to each stress session and prior to testing	CUS	Prevention/ rescue (SS)	
Citalopram	SSRI	5 mg/kg (s.c.)	Acute, prior to reversal	CIC	Rescue (RL)	Lapiz-Bluhm et al. (2009)
Desipramine	Norepinephrine reuptake blocker	7.5 mg/kg/day (i.p. pump)	Chronic, 7 days prior to stress, prior to each stress session and prior to testing	CUS	No effect (RL) Prevention (SS)	Bondi et al. (2008)
Escitalopram	SSRI	5 mg/kg/day (i.p pump)	Chronic, 7 days prior to stress, prior to each stress session and prior to testing	CUS	No effect (RL) Prevention (SS)	
Ketamine	Non-competitive NMDA receptor antagonist	10 mg/kg (i.p.)	Acute, 24 h prior to testing	CUS	No effect (RL) Rescue (SS)	Jett et al. (2015)
Vortioxetine	Multimodal-acting antidepressant	30 or 90 mg/kg (in chow)	Chronic, 7 days prior to stress, prior to each stress session and prior to testing	CIC	Prevention/ rescue (RL)	Wallace et al. (2014)
Citalopram	SSRI	5 mg/kg (i.p.)	Acute, prior to reversal	CIC	Rescue (RL)	Danet et al. (2010)
Desipramine	Norepinephrine reuptake blocker	5 mg/kg (i.p.)	Acute, prior to reversal	CIC	No effect (RL)	
Norepinephrine antagonist cocktail	α1, β1, and β2 receptor antagonist	0.5 µl/side (mPFC infusion)	Repeated, prior each CUS session	CUS	No effect (RL) Prevention (SS)	Jett and Morilak, 2013
Atipamezole HCl	α2 receptor antagonist	1 mg/kg (i.p)	Acute, prior to testing	CUS	Rescue (R1, SS) No effect (R3)	Bondi et al. (2010)
Desipramine	Norepinephrine reuptake blocker	7.5 mg/kg/day (mPFC infusion)	Repeated, 7 days prior to stress, prior to each stress session and prior to testing	CUS	Prevention (RL, SS)	
Benoxathian	α1 receptor antagonist	2 nM (mPFC infusion)	Acute, prior to set-shifting	CUS	No effect (SS)	
Desipramine and benoxathian	Norepinephrine reuptake blocker and α1 receptor antagonist	7.5 mg/kg/day desipramine + 2 nmol benoxathian (mPFC infusion)	Repeated desipramine acute benoxathian	CUS	No effect (SS)	
21 days						
Amantadine	NMDA receptor antagonist	25 mg/kg (gavage)	Repeated, daily from day 4 to day 23 of CUS	CUS	Prevention (RT) Partial prevention (RL)	Yu et al. (2015)
HU-210	CB_1 receptor agonist	10 µg/kg	Acute, prior to reversal	CUS	Rescue (RL)	Hill et al. (2005)

Table 3 (*continued*)

Drug	Mechanism	Dose	Administration	Stressor	Performance change	Reference
35 days						
Citalopram	SSRI	20 mg/kg/day (i.p pump)	Chronic, daily from day 15 to day 35 of CIC	CIC	Prevention (RL)	Danet et al. (2010)
Desipramine	Norepinephrine reuptake blocker	7.5 mg/kg/day (i.p pump)	Repeated, daily from day 15 to day 35 of CIC	CIC	No effect (RL)	

testing, 30-ng CRF infusions impaired reversal learning but had no effect on set-shifting (Snyder et al., 2015b).

The relationship between the HPA axis and SNS has also been studied by infusing CRF into the locus coeruleus. Following a CRF infusion, neurons within the locus coeruleus had an elevated discharge rate and mPFC NE levels were augmented (Curtis et al., 1997). Further, this infusion altered ASST performance by facilitating ED set-shifting at low doses and enhancing reversal learning at higher ones (Snyder et al., 2012). These behavioral changes were not observed following intraventricular CRF administration suggesting the enhancements were the result of specific changes in locus coeruleus functioning (Snyder et al., 2012). Taken together, these experiments support a role of CRF in the modulation of other neurotransmitter systems and that ultimately lead to changes in behavioral flexibility following stress.

The role of corticosterone has also been tested in several studies. In an acute or 3-day stress paradigm, systemic administration of either a glucocorticoid or mineralocorticoid receptor (MR) antagonist failed to alter the improvement in reversal learning following stress (Thai et al., 2013; Bryce and Howland, 2015). In contrast, inhibiting corticosterone synthesis prior to daily repeated stress prevented set-shifting impairments that normally followed repeated restraint stress (Nikiforuk and Popik, 2011). Therefore, enhanced reversal learning following acute stress may occur independently of glucocorticoid and MR activation, which differs from repeated stress, where behavioral flexibility impairments appear to require corticosterone at the time of the stressor.

Catecholamines

The availability of NE within the mPFC plays a critical role in set-shifting and may modulate the effects of stress. During stress exposure, locus coeruleus activity increased in adult rats suggesting the NE pathway is activated by stress application (Zitnik et al., 2016). Further, pharmacological lesions of the dorsal adrenergic ascending bundle effectively prevent signaling from the locus coeruleus to the mPFC and impair ED set-shifting (Tait et al., 2007). Neural activity in the locus coeruleus is also altered in stressed rats during behavioral flexibility performance. In control rats, neurons reach the greatest firing rate between correct response selection and reward administration whereas maximal rates occur only following reward in stressed rats. This shift from task-responsive to reward-responsive firing was specific to reversal learning and ID set-shifting. Interestingly, these are the two components of the ASST that showed stress-induced facilitation (Chaijale et al., 2015).

The role of NE in behavioral flexibility following stress has also been examined in a series of complicated pharmacological studies (Fig. 4; Table 3). Drugs that inhibit the reuptake of neurotransmitters prevent the removal of the neurotransmitter from the synapse, thereby increasing its availability and signaling effects. Repeated treatment with desipramine, a NE reuptake inhibitor, or milnacipran, a 5-HT-NE reuptake inhibitor, selectively attenuates stress-induced ED set-shifting impairments (Bondi et al., 2008; Naegeli et al., 2013). These findings raise the possibility that reduced NE availability may underlie the effects of stress on ED set-shifting; however, rats exposed to chronic unpredictable stress have similar levels of NE in the mPFC as controls but impaired set-shifting (Bondi et al., 2010). Thus, the rescue of stress-induced ED set-shifting impairments following NE reuptake inhibitors may also be a consequence of the activation of distinct noradrenergic receptor subtypes, rather than increased NE availability per se. For example, the rescue of stress-induced set-shifting impairments following repeated desipramine treatment is prevented by acute infusion of an α_1 receptor antagonist into the mPFC (Bondi et al., 2010). In separate experiments that did not involve desipramine, the behavioral flexibility impairments resulting from stress exposure were prevented by pretreatment with an α_1, β_1, and, β_2 receptor antagonist cocktail but not an α_1 receptor antagonist alone (Bondi et al., 2010; Jett and Morilak, 2013). Thus, although α_1 receptor activation appears necessary for the beneficial effects of increased NE availability, α_1 receptors are not intrinsically required for set-shifting. In contrast, acute treatment with α_2 receptor antagonists rescues stress-induced R1 deficits following stress (Bondi et al., 2010). Similarly, acute administration of an α_2 antagonist following stress rescued ED set-shifting performance. However, this facilitation was prevented by mPFC infusion of an α_1 antagonist (Lapiz and Morilak, 2006). Overall, these studies suggest impaired behavioral flexibility following stress may relate to post-synaptic changes in NE receptor activation.

Dopamine is involved in behavioral flexibility, perhaps through its role in facilitating rule incorporation and suppression. Acute stress exposure leads to rapid dopamine release within the mPFC (Finlay et al., 1995; Butts et al., 2011). This release depends upon corticosterone and is prevented by GR antagonism (Butts et al., 2011). Infusions of a D1 antagonist into the mPFC increases perseverative and never-reinforced errors dur-

ing set-shifting (Ragozzino, 2002). Within the context of repeated stress, acute D1 agonist administration prior to behavioral flexibility testing influences performance in a dose-dependent manner. Control and stressed rats demonstrate facilitated ED set-shifting following SKF 81297 administration at a dose of 0.1–0.3 mg/kg or 0.01–0.1 mg/kg respectively (Nikiforuk, 2012b). This suggests that heightened dopamine activity enhances flexibility and stressed animals may be more sensitive to these increases. The effects of D1 receptor activation depend upon the route of administration, with facilitated performance following intraperitoneal injections but not mPFC or nucleus accumbens infusions (Floresco et al., 2006; Haluk and Floresco, 2009). This demonstrates that set-shifting enhancement may require increasing activation of dopamine receptors in several cortical and non-cortical structures.

Serotonin

5-HT plays a role in altered reversal learning and set-shifting performance following stress (Fig. 4; Table 3). Pharmacologically inhibiting 5-HT synthesis impairs reversal learning within the ASST, mirroring the effects of repeated stress (Lapiz-Bluhm et al., 2009). 5-HT transporter knockout mice make fewer perseverative errors and total errors during ED set-shifting and reversal learning respectively, as compared to control mice (Nonkes et al., 2012). Taken together, lower 5-HT levels contribute to reduced behavioral flexibility, suggesting that increasing 5-HT levels may facilitate behavioral flexibility performance following stress. In support of this hypothesis, acute administration of a selective 5-HT reuptake inhibitor, citalopram, prevented repeated intermittent cold stress reversal learning deficits (Lapiz-Bluhm et al., 2009; Danet et al., 2010). Alleviation of R1 impairments was also observed when citalopram began the 3rd week of a 5-week repeated intermittent cold stress paradigm (Danet et al., 2013). However, a different selective 5-HT reuptake inhibitor, escitalopram, prevented ED set-shift impairments but did not change reversal learning performance within the chronic unpredictable stress paradigm (Bondi et al., 2008). Other drugs, such as the multimodal antidepressant vortioxetine, have varying effects on 5-HT receptor subtypes and transporters. Treatment with vortioxetine throughout a chronic intermittent cold stress paradigm reduced reversal learning impairments on the ASST (Wallace et al., 2014). Lastly, acute administration of a 5-HT_7 receptor antagonist prior to ED set-shift testing rescues performance following 7 days of restraint stress (Nikiforuk, 2012a). Therefore, 5-HT is necessary for reversal learning under stress-free conditions and its enhancement is capable of alleviating behavioral inflexibility in ways which may depend upon the stress paradigm.

Other neurotransmitters

Other neurotransmitters have been implicated in the effects of stress exposure on behavioral flexibility. Acute stress increases PFC glutamate function by increasing N-methyl-D-aspartate (NMDA) receptor and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor trafficking (Yuen et al., 2011), which suggests that reduced glutamate receptor function may rectify stress-induced inflexibility. Ketamine, a non-competitive NMDA receptor antagonist, that was administered prior to each stress session in a 7-day restraint paradigm prevented set-shifting impairments (Nikiforuk and Popik, 2014). Acute ketamine administration selectively rescues ED set-shifting, but not reversal learning, following chronic unpredictable stress (Jett et al., 2015). Chronic administration of the NMDA receptor antagonist amantadine recovers reversal training and aspects of testing within the Morris Water Maze task following chronic unpredictable stress (Yu et al., 2015). The inconsistent effects of NMDA receptor antagonists may be a consequence of drug, drug repetition, stress type or stress duration. Finally, brain-derived neurotropic factor and cannabinoids may rescue behavioral flexibility following stress but further research is needed in this area (Hill et al., 2005; Graybeal et al., 2011; Jett et al., 2015).

CONCLUSIONS

The present review details the effects of stress on behavioral flexibility. These effects are complex and depend on a variety of factors including the type and duration of the stressor, the sex and strain of the subject, and the flexibility paradigm. When stress was repeated once or for few sessions, it appears to have the capacity to facilitate reversal learning but only following relatively mild stress (Graybeal et al., 2011; Thai et al., 2013; Graybeal et al., 2014; Bryce and Howland, 2015; George et al., 2015). Due to the limited number of studies conducted and the variability between methods this may be a simplification, and other factors such as length of stress as well as testing paradigm may interact with the stressor type and session number to produce varying effects. For example, although the stressors with shorter durations tended to produce beneficial effects, this time window may fall within a small range and very short stressors may have no effect on performance. In contrast, only one of the identified studies reported improved set-shifting following stress (Chaijale et al., 2015). The two subtypes of set-shifting are affected distinctly, with ID set-shift capabilities appearing relatively resistant to stress compared to ED set-shifts. Repeated stress also appears to alter behavioral flexibility in a manner that depends upon the stressor. Specifically, chronic intermittent cold stress consistently impairs reversal learning without affecting set-shifting whereas chronic unpredictable stress impairs reversal learning and set-shifting. This may be due to several factors including the stress paradigm itself or the duration of each stress session, as cold stress was 6 h daily whereas chronic intermittent stress varied depending on the stressor.

Table 3 details the modulation of different neurotransmitter systems on behavioral flexibility following stress. The prevention of the effects of stress or the rescue of flexibility performance following stress depends upon the stressor characteristics. Corticosterone may be necessary for impairments in

set-shifting to manifest after repeated restraint stress (Nikiforuk and Popik, 2011; Thai et al., 2013). Catecholamines also seem to contribute to stress-induced inflexibility as enhanced NE function within the mPFC and D1 agonist administration rescue performance (Nikiforuk, 2012b). 5-HT is necessary for reversal learning in unstressed animals and increasing its availability facilitates reversal learning and set-shifting in stressed animals (Lapiz-Bluhm et al., 2009; Nikiforuk, 2012a).

This review has several important implications for the study of stress effects on behavioral flexibility. First, our review suggests a need for a more standardized experimental approach to allow for comparisons among studies and a more thorough understanding of the implications of stress for behavioral flexibility. Second, gaps in the existing literature have been identified including questions regarding potential sex differences, the role of corticosterone and its receptors in the effects of stress, and why certain stress manipulations only affect either reversal learning or set-shifting. Finally, this review demonstrates a number of mechanisms underlying the effects of stress on flexibility. Given the role of stress in psychiatric disorders, including depression and post-traumatic stress disorder, these findings may inform the development of treatment strategies for patients with impaired cognitive flexibility.

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