EFFORT-BASED DECISION MAKING IS SENSITIVE TO THE EFFECTS OF
ACUTE STRESS

by

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Abstract

Acute stress can either exert beneficial or detrimental effects on different forms of cognition, and these effects may be mediated in part by enhanced glucocorticoid and dopaminergic activity. Recent studies in humans have shown that acute stress disrupts certain aspects of cost/benefit decision making. In the following series of experiments, we assessed the effects of acute restraint stress on different forms of cost/benefit decision making, and some of the hormonal and neurochemical mechanisms that may underlie these effects. Effort-based decision making was assessed with a discounting task where rats chose between a low effort/reward lever (1 press=2 pellets), or a high effort/reward lever that delivered 4 pellets, with the effort requirement increasing over 4 blocks of discrete trials (2, 5, 10, and 20 presses). A single exposure to 1 hour stress decreased preference for the high effort/reward and increased response latencies. Control experiments revealed that these effects did not appear to be mediated by general decreases in motivation or reduced preference for larger rewards. A separate group of rats were trained on delay discounting task where they chose between a small/immediate reward (1 pellet) or a larger, 4 pellet reward delivered after a delay (0, 15, 30, 45 sec). In contrast to effort discounting, acute stress did not affect choice of larger, delayed rewards. The role of glucocorticoids in regulating effort-based decision making was assessed via the systemic administration of exogenous corticosterone (1 or 3 mg/kg). These treatments failed to mimic the effects of stress on effort discounting. In a final experiment, dopamine receptor blockade with flupenthixol (0.25 mg/kg) prior to restraint to did not attenuate the stress-induced effects on effort-related choice. However, this treatment abolished the stress-induced increase in response latencies. These data suggest that acute
stress interferes somewhat selectively with cost/benefit evaluations concerning rewards of
different magnitudes and the relative effort costs associated with obtaining them. These
effects do not appear to be mediated by enhanced glucocorticoid activity, whereas
dopaminergic activation may contribute to increased latencies induced by stress. These
findings may provide insight on impairments in decision making and anergia associated with
stress-related disorders such as depression.
Preface

Research for this thesis was approved by the UBC Animal Care Committee, application number A10-0197
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List of Abbreviations

Corticosterone (CORT)
Corticotropin releasing hormone (CRH)
Dopamine (DA)
Fixed-ratio (FR)
High effort/reward (HR)
Low effort/reward (LR)
Norepinephrine (NE)
Nucleus accumbens (NAc)
Prefrontal cortex (PFC)
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This one's for me
Introduction

Acute stress evokes numerous hormonal, physiological and neural responses that are designed to reorganize energy utilization and cognitive/behavioural functioning to promote adaptive responses and attain some form of homeostasis. Detection of an acute stressor activates the hypothalamic-pituitary-adrenal axis, characterized by the release of brain corticotropin releasing hormone (CRH) and then, adrenocorticotropic hormone from the pituitary, which in turn stimulates the release of glucocorticoids, a steroid hormone which exerts multiple effects on the body and brain (Tsigos & Chrousos, 2002).

The release of CRH in the brain and glucocorticoids from the adrenal glands can affect different aspects of neural functioning, cognition and behavior by activation of their receptors localized within different regions of the brain, but also through modulation of other neurotransmitter systems. CRH stimulates the release of monoamine transmitters, including norepinephrine (NE) from the locus ceruleus and mesolimbic dopamine (DA) from the ventral tegmental area. Conversely, the release of glucocorticoids (cortisol in humans, corticosterone (CORT) in rats) can inhibit sustained release of CRH and NE through negative feedback loops (Tsigos & Chrousos, 2002). These neurochemical alterations are believed to be one mechanism through which stress may alter different aspects of cognition.

Acute stress has been shown to exert either detrimental or beneficial effects on different variety of learning, memory and cognition, depending on numerous factors such as the severity of the stressor, task difficulty and the specific brain systems that are involved. Studies in rats as well as humans have both reported an abundance of glucocorticoid receptors in the hippocampus (de Kloet & Reul, 1987; Funder & Sheppard, 1987; Seckl et al, 1991), and other limbic structures, as well as the prefrontal cortex (PFC) (Putman et al,
2010). Not surprisingly, types of cognition mediated by these glucocorticoid receptor-rich regions are stress-sensitive. Rodent studies using either the Morris water maze or radial arm mazes have shown that acute stress can impair hippocampal-dependent spatial memory (de Quervain et al, 1998; Diamond & Rose, 1994; Kim et al, 2007). Alternatively, acute stress can also enhance amygdala-dependent associative learning and classical conditioning (Shors et al, 1992; Joël et al, 2006), in addition to facilitating contextual fear conditioning in rats (Cordero et al, 2003). More complex forms of cognition mediated by the frontal lobes are also sensitive to acute stress. In humans, stress induced through the Trier Social Stress Test impairs PFC-dependent working memory without affecting verbal explicit or implicit memory for neutral stimuli (Luethi et al, 2008). Similar impairments in working memory have been observed in laboratory animals using restraint stress (Stillman et al, 1998; Shansky et al., 2006) or the pharmacological stressor FG712 that increases release of dopamine in the prefrontal cortex (Murphy et al, 1996a; 1996b). However, the effect of glucocorticoids on working memory shows an inverted-U dose response pattern (Lupien & McEwen, 1997), as mild stressors can have beneficial effects on working memory (Yuen et al, 2009). Thus, the effects of acute stress on cognitive performance are dependent on a variety of factors, including the type of task, the specific brain circuitry that is recruited by these tasks, and the severity of the stressor.

Stress-induced impairments in PFC-related cognition are thought to be attributable in part to excessive increases in DA release within this region. Psychopharmacological studies have revealed that dopaminergic modulation of PFC function takes the form of an “inverted U” shaped curve, in that too little or too much PFC DA activity may impair functions such as working memory (Arnsten, 1997; Floresco & Magyar, 2006; Vijayraghavan et al, 2007).
With respect to acute stress and PFC DA release, microdialysis studies have shown a selective increase in extracellular DA levels of the PFC in response to a wide number of stressors, including tail pinch/shock (Abercrombie et al, 1989; Finlay et al, 1995), restraint stress (Imperato et al, 1989; 1991) and footshock (Roth et al, 1988; Davis et al, 1994). Increases in PFC DA occur both in response to the initiation as well as the termination of restraint stress (Imperato et al, 1991). Interestingly, adrenalectomy or administration of a CORT antagonist do not attenuate restraint-stress induced DA release, suggesting that central mechanisms independent of hypothalamic-pituitary-adrenal axis activation may be driving stress induced increases in PFC DA (Imperato et al, 1991). Moreover, pharmacological manipulations that either directly or indirectly block increases in PFC DA activity induced by stress attenuate the impairments in working-memory induced by these stressors (Murphy et al, 1996a; 1996b). These latter findings indicate that impairments in working memory and increases in PFC DA induced by acute stress are causally-related phenomena.

Although the effects of acute stress on working memory functions subserved by the PFC have been fairly well characterized, there has been substantially less research on how stress may affect other more complex forms of cognition mediated by the frontal lobes. In particular, how stress may affect different aspects of cost/benefit decision making remains relatively unexplored. Some of the pioneering research on the topic stemmed from the observations that highly-skilled pilots fell victim to battle-induced mental errors and poor decision making during these stressful circumstances (Broadbent, 1971). It is now understood that under conditions of acute stress, flexible decision making dependent on normal PFC functioning is impaired (Arnsten, 1998), causing an organism to rely more on habitual behavior (Elliott & Packard, 2008). Recent laboratory studies in humans have begun
to investigate how acute stress may alter decision making on a variety of gambling tasks designed to simulate real-life decisions in terms of uncertainty, reward and punishment. These studies have revealed that either acute cold stress or the administration of exogenous glucocorticoids impair decision making, by either decreasing the net gain of the subject over the session or biasing the choice towards the riskier option when the chances of losing are higher (Miu et al, 2008; Porcelli & Delgado, 2009; Putman et al, 2010). These studies suggest that acute stress may alter the manner in which individuals evaluate the relative costs and benefits associated with different options, sometimes leading them to make more disadvantageous choices.

Recent work investigating the neurobiological basis underlying different forms of decision making in experimental animals has expanded our understanding of the neural circuitry that mediates different forms of judgments, and would thus be particularly useful in clarifying how acute stress may interfere with these processes. In these studies, animals evaluate the cost of competing response options relative to the potential reward that may be obtained; a key component of decision making tasks used in humans. For example, in “delay-discounting” tasks, response costs are varied by imposing a delay before delivery of a larger reward versus acquiring an immediate, smaller reward. Alternatively, in “effort-based” decision making, animals choose between a small reward obtainable after a nominal amount of physical effort, or obtaining a larger reward after considerably more work than the former option (e.g.; climbing a barrier, pressing a lever multiple times).

The neurobiological basis of effort-based decision making has been studied in some detail, and has been shown to be mediated by an interconnected neural network that includes the temporal, frontal, forebrain and midbrain regions. Animal models have shown that either
excitotoxic lesions or reversible inactivations of the anterior cingulate of the medial PFC (Walton et al., 2002; Walton et al., 2003; Schweimer & Hauber, 2005), the basolateral amygdala (Floresco & Ghods Sharifi, 2007; Floresco et al, 2008b; Ghods-Sharifi et al, 2009) as well as the nucleus accumbens (NAc) of the ventral striatum (Cousins & Salamone, 1994; Salamone et al, 2003; 2005) reduce the preference for rats to work harder in order to obtain a larger reward. Furthermore, DA also plays a role in overcoming reward associated costs. Decreasing DA activity through either localized neurotoxic depletion or administration of DA antagonist in the PFC as well as the NAc also lessens the choice of the higher effort/reward (HR) option in the various versions of the effort judgment task (Cousin & Salamone, 1994; Salamone et al, 1991; 2006; Schweimer & Hauber, 2005). Interestingly, increasing DA activity through the administration of psychostimulant drugs such as amphetamine exerts differential dose-dependent effect. While low doses increase the selection of the HR, higher doses of the same drug reduce preference for the HR (Floresco et al, 2008b). In contrast, serotonin (another monoamine system activated by acute stress (Kawahara et al, 1993)) does not appear to play a role in this form of decision making. Rather, serotonin depletion decreases preference for larger, delayed rewards without altering performance on the effort-based decision making task (Denk et al, 2005). These findings indicate that effort-based decision making is mediated by a distributed neural circuit incorporating the amygdala, the forebrain and the DA system.

Activity in the above-mentioned systems that contribute to effort-based decision making is particularly sensitive to acute stress, and other cognitive functions subserved by these systems have been shown to be altered by exposure to acute stressors (Shors et al, 1992; Diamond & Rose, 1994; de Quervain et al, 1998; Stillman et al, 1998; Cordero et al,
Therefore, the possibility remains that acute stress may interfere with effort-related decision making as it does with other types of cognition in animals and other forms of decision making in humans.

To investigate this in more detail, the present study assessed the effects of acute restraint stress on effort-based decision making, using a discounting operant task previously described by Floresco and colleagues (2008b; 2009). Restraint is a well-characterized method of inducing mild, but considerable stress in laboratory rodents. This approach has been shown to reliably increase circulating levels of stress-associated hormones, including adrenocorticotropic hormone and CORT (Kant et al, 1983; Kant et al, 1987) without causing any severe pain or enduring discomfort to the animal. Furthermore, restraint stress has been shown to disrupt cognition in rats (Shansky et al, 2006; Cordero et al, 2003), and induce reliable increases in DA release within the PFC and ventral striatum (Roth et al, 1988; Abercrombie et al, 1989; Imperato et al, 1989; 1991; Finlay et al, 1995; Davis et al, 1994). An initial experiment revealed that restraint stress altered effort discounting. Accordingly, subsequent experiments were conducted to clarify the specific cognitive/motivational processes that were affected by stress, which may have contributed to the alterations in decision making. Furthermore, we also investigated some of the hormonal and neurochemical mechanisms that may underlie these effects, specifically looking at the contribution of CORT and DA to the effects of stress on this form of decision making.
General Methods

Animals

Different cohorts of male Long Evans rats (Charles River Laboratories, Montreal, Canada) weighing 275-300g at the beginning of training were used. Upon arrival, rats were given 1 week to acclimatize to the colony conditions, and subsequently individually housed and food restricted to 85-90% of their free feeding weight 1 week prior to behavioral training. Water was provided *ad libitum* for the duration of the experiment. Body weights were monitored daily, and food was provided in the animal’s home cage at the end of each experimental day. All testing was done in accordance with the Canadian Council of Animal Care and the Animal Care Committee of the University of British Columbia.

Apparatus

All behavioral testing was conducted in operant chambers (30.5 x 24x 21cm; Med-Associates, St Alban, VT, USA) enclosed in a sound-attenuating box. Boxes were equipped with a fan that provided ventilation and masked extraneous noise. Each chamber was fitted with two retractable levers, one located on each side of a central food receptacle where food reinforcement (45 mg; Bioserv, Frenchtown, NJ) was delivered by a pellet dispenser. The chambers were illuminated by a single 100-mA house light located in the top center of the wall opposite the levers. Four infrared photo beams were mounted on the sides of each chamber, and another photo beam was located in the food receptacle. Locomotion activity was indexed by the number of photo beam breaks that occurred during a session. All experimental data were recorded by a personal computer connected to the chambers through an interface.
Initial lever training

Our initial training protocol has been described previously (Floresco et al, 2008a; Ghods-Sharifi et al, 2009). On the day prior to the first exposure to the operant chamber, rats were given ~ 20 reward pellets in their home cage. Before the animal was placed in the chamber for the first training session, 2-3 crushed pellets were placed inside of the food receptacle and on the active lever. Rats were trained under a fixed-ratio (FR)- 1 schedule to a criterion of 60 presses in 30 minutes, first for one lever, then the other (counterbalanced left/right between subjects). On subsequent days, rats were trained on a simplified version of the full task where they had to act upon a retractable lever within 10 sec of insertion. These sessions consisted of 90 training trials and began with both levers retracted and the chamber in darkness. Every 40 sec, a trial was initiated with the illumination of the houselight and the extension of one of the two levers. If the rat failed to respond on the lever within 10 sec after lever insertion, it was retracted, the chamber returned to darkness, and the trial was scored as an omission. A response on the lever within 10 sec of its insertion delivered one reward pellet. Rats were trained for ~5 days to a criterion of 80 successful trials (i.e., <10 omissions), after which they were trained on the decision making task.

Effort discounting

Each training day, animals received one 32 min session that consisted of 48 discrete trials, separated into 4 blocks. A session began with the chamber in darkness and both levers retracted (the intertrial state). At 40 sec intervals, trials commenced with the illumination of the houselight, followed by the extension of one or both levers 3 sec later. Each of the 4 blocks of trials began with two forced-choice trials, where only one of the two levers was randomly presented. During the next 10 trials, both levers were presented and the animal
chose between the two levers. One lever was designated as the Low Reward (LR) lever, and the other lever was designated as the HR lever. These levers were counterbalanced (left/right) between animals, and remained constant for each animal for the duration of the experiment. Once the levers were presented, the rat was required to make a response within 25 sec; a failure to do so was scored as an omission, and the chamber was reset to the intertrial state. A single press of the LR lever resulted in the retraction of both levers and the immediate delivery of two pellets. However, after the first response on the HR lever, the LR lever was immediately retracted, and the HR lever remained inserted in the chamber until the required ratio of presses were completed. The ratio requirement for the HR lever increased within the session (described below). Upon completion of the required effort ratio on the HR lever, the lever retracted and four pellets were delivered 0.5 sec apart. The houselight remained on for another 4 sec after the delivery of the last pellet. The chamber then darkened, and was reset to the intertrial state (see Fig 1).

The fixed effort ratio of lever presses required to obtain the HR increased over the 4 blocks of trials, beginning with 2 presses, then 5, 10, and finally 20 presses respectively. On the rare occurrence when a rat failed to complete the required number of presses on the HR lever within 25 sec after its insertion, the lever retracted without delivery of any food, and the chamber was reset to the intertrial state. However, the animal’s choice was still incorporated into the data analysis. In addition, the amount of time taken for a rat to initiate a lever press as well as the latency to complete the required number of presses on the HR lever once a choice was made were recorded.
Figure 1. Schematic of the effort-based decision making task. (A) The format of a single free-choice trial on the effort discounting task. (B) Cost/benefit contingencies associated with either lever.
Rats were trained on the effort discounting task 5-7 days a week until as a group, they 1) chose the HR lever during the first trial block on at least 75% of successful trials, and 2) demonstrated stable baseline levels of discounting for 3 consecutive days. Stability was assessed using statistical procedures similar to that described by Winstanley and colleagues (2004), Floresco and colleagues (2008b) and St. Onge and Floresco (2009). In brief, data from three consecutive sessions were analyzed using a repeated-measures ANOVA with two within-subjects factors (Training Day and Trial Block). If the effect of Block was significant at the \( p<0.05 \) level but there was no main effect of Day or Day x Trial Block interaction (at \( p>0.1 \) level), animals were judged to have achieved stable baseline levels of choice behavior. They then received their first stress test day.

**Restraint stress**

Acute stress was induced by subjecting rats to restraint in a plexiglas semi-cylindric tube (83 x 133 x 197 mm; Harvard Apparatus, Massachusetts, USA) in a quiet, lit and ventilated room. Rats were placed in the tubes, and the restrainer length was adjusted to keep the rat immobilized, but without causing pain to the animal. A desktop fan circulated air over the restraint tubes while animals were being stressed to minimize hyperthermia that can be induced by these manipulations. Upon being removed from the restraint tube, animals were returned to their homecages in which they were left undisturbed for 10 minutes prior to being placed in the operant chambers. In the first experiment, rats received two counterbalanced restraint stress sessions of differing durations (20 min or 1 hour) on separate test days. In all other experiments, only the 1 hour duration of restraint was used. For all experiments, 1-2 days prior to a stress test session, rats (in their homecages) were placed in the same room where stress manipulations would take place on the following day. They were left in the
room for the amount of time corresponding to the duration of the stressor they would receive on the following day (20 min or, for most experiments 1 hour). There were no statistically significant differences in behaviour across experiments between training sessions where animals were placed in the stress-procedure room when compared to the regular training sessions. Therefore, baseline control data for all behavioural measures were obtained by computing an average of the particular measure recorded over the last two days prior to stress, which included data taken from a regular training session, and a session preceded by being placed in the stress-procedure room without restraint. These baseline values served as the key control data for which within-subjects statistical comparisons were made. For experiments where animals received multiple stressors, these tests were separated by at least 7 days.
Results

Experiment 1: The effect of 20 min or 1 hour restraint stress on effort discounting

The primary aim of this experiment was to determine whether acute restraint stress alters different aspects of effort-based decision making. A secondary aim was to determine if there is a “threshold” of stress duration that would affect decision making. Rats (n=14) were trained for 22 days on the effort discounting task, after which they displayed stable levels of choice behaviour. They subsequently received the first of two counterbalanced stress tests of either 20 min or 1 hour in duration. After the first session of restraint, rats were retrained for 7 days before receiving their second stress test. Baseline levels of choice of the HR lever prior to the 20 min or 1 hour stress test day did not differ. Thus, the average of these two values was used for the data analysis. Restraint stress induced a marked decrease in the preference to work harder for a larger reward. Choice data were analyzed with a three-way between/within subjects ANOVA, with Order of stress duration (20 min or 1 hour restraint) as a between subjects factor, and Test Day (baseline, 20 min or 1 hour stress) and Trial Block as two within-subjects factors. This analysis revealed a significant effect of Test Day ($F_{2,24}=7.94$, $p<0.005$), but not a significant Test Day x Trial Block interaction ($F_{6,72}=1.15$, n.s.). Multiple comparisons confirmed that 1 hour, but not 20 min of restraint stress significantly ($p<0.05$) decreased choice of the HR lever relative to baseline (Fig 2A). This effect was apparent in the first trial block, and persisted over the duration of the session. Notably there was no main effect of Order of stress duration, or any interactions with the within subjects factors (all $F$s<2.27, n.s.), indicating that rats initially exposed to 20 min stress showed alterations in behaviour after 1 hour stress that were comparable to rats that received 1 hour stress on the first stress test.
Figure 2. Effort discounting following acute restraint stress. Effects of acute restraint stress (1 hour and 20 min) on effort discounting. (A) The ordinate shows the percent choice of the HR lever across the four trial blocks and the abscissa indicates the four trial blocks with increasing effort ratio. 1 hour and not 20 min restraint decreased the selection of the HR option across all trial blocks. (B) The response latency across trial blocks. 1 hour restraint increased the latency to respond in the third and fourth trial block. (C) Acute restraint stress did not affect the rates of pressing on the HR lever. Stars identify significant main effect at \( p<0.05 \).
In addition to reducing preference for the higher effort option, acute stress also increased the latencies to make a choice. These data were analyzed in a manner similar to the choice data, and revealed a significant Test day x Trial Block interaction (F_{6,72}=2.670, \( p=.021 \)), although the main effect of Test day was not significant (F_{2,24}=1.74, n.s.; Fig 2B). Simple main effects analysis confirmed that 1 hour (but not 20 min) restraint significantly increased choice latencies during the last two trial blocks when the effort requirements on the HR lever were 10 and 20 presses respectively. Again, there was no main effect of Order, or any interactions with the within subjects factors (all Fs<1.17, n.s.).

The stress-induced increase in response latency was not associated with a change in the average rates of lever pressing (press/sec) on the HR lever (F_{2,24}=1.02, n.s.; Fig 2C). Thus, even though 1 hour stress decreased the overall preference for the HR lever, on trials where rats choose this option, they responded on the HR lever as robustly as they did after 20 min of stress or on baseline days. In this experiment, locomotor activity was decreased on stress test days when compared to baseline, but the overall analysis of these data with a one-way ANOVA did not reveal an overall significant effect (baseline: 1017 +/- 119, 20 min: 927 +/- 115, 1 hour: 855, +/-135, F_{2,24}=2.65, \( p=0.09 \)). Furthermore, stress did not increase the number of trial omissions (baseline: 0.48 +/- 0.21, 20 min: 1.21 +/-0.85, 1 hour: 1.86, +/-1.036; F_{1,13}=0.002, n.s.). Collectively, these data suggest that 1 hour of restraint stress causes a substantial decrease in the preference for animals to work harder to obtain a larger reward, and also increases deliberation times when the HR option is associated with a relatively high effort cost.
**Experiment 2: The effect of acute stress on reward magnitude discrimination**

Experiment 1 revealed that acute stress decreases the preference to work harder to obtain a larger reward. There are a number of possible explanations for this effect. For example, acute stress may have caused a decrease in the subjective preference for objectively larger versus smaller rewards. This possibility was investigated in Experiment 2, which assessed the effects of acute stress on a reward magnitude discrimination task. If the stress induced preference away from the HR option is a reflection of decreased preference for more food, using this protocol, restraint stress should decrease the preference for a larger reward even when this option is not associated with a higher cost.

**Methods**

A group of 8 rats received initial lever press training in a manner similar to that used in Experiment 1. Subsequently, they received daily training sessions on a reward magnitude discrimination task previously described by Ghods-Sharifi and Floresco (2010). This task was nearly identical to the effort discounting task (i.e: 48 trials, 4 trial blocks, 2 forced choice/10 free choice trials per block, 40 sec intertrial interval), with one key exception. Here, a single press of either the LR or HR lever caused the immediate delivery of either 2 or 4 pellets. Thus, animals merely had to choose between a smaller or larger reward, with no additional cost associated with the larger reward option. Rats were trained for 9 days, after which they displayed a strong preference for the HR lever (~90%). They were subsequently subjected to a baseline session, followed by a 1 hour restraint stress challenge on the next day. For this and all subsequent experiments, we only used 1 hour restraint as a stressor, as this was the only duration of stress tested that was effective at altering choice behaviour and response latencies on the effort discounting task.
Results

Stress did not decrease the preference for the HR option. Analysis of the choice data showed no significant main effect of Test Day (F_{1,7}=1.577, n.s.) or Test Day x Trial Block interaction (F_{3,21}=1.56, n.s.; Fig 3A). However, as was observed in Experiments 1, acute stress did increase response latencies (main effect of Test Day; F_{1,7}=16.837, p=0.005; Test Day x Trial Block interaction; F_{3,21}=1.836, n.s.; Fig 3B). Thus, despite not altering the choice between a large versus small reward, acute stress was effective at increasing choice latencies.

Locomotor activity was not altered by acute stress relative to baseline in this experiment (baseline: 727 +/- 109, 1 hour: 783 +/- 124; F_{1,7}=0.006, n.s.). Furthermore, stress did not alter the number of trial omissions (baseline: 0, 1 hour: 0). These data suggest that acute stress does not disrupt the general preference for larger versus smaller rewards, but deliberation times to make a selection under these relatively simpler conditions were increased following acute stress exposure.

Figure 3. Reward magnitude discrimination following acute restraint stress Effects of acute restraint stress on performance in a reward magnitude discrimination task. (A) Acute restraint stress did not alter preference for the HR option when there was no additional cost associated with it. (B) Response latencies across each block of 10 free-choice trials (left) and averaged across the four trial blocks (right). Acute restraint stress increased the latency to make a choice. Stars identify significant main effect where p<0.05.
Experiment 3: The effect of acute stress on effort discounting with equivalent delays

With the effort discounting task used in Experiment 1, when animals choose the high effort option, the amount of time it takes to complete the ratio of presses on the HR lever imposes a delay from the time of the initial choice to when the reward is delivered. Therefore, it is possible that the decrease in the preference for the HR option induced by 1 hour stress may reflect decreased tolerance for delayed rewards rather than a decreased tolerance towards greater effort demands. One manner to evaluate this hypothesis is to employ an equivalent delay procedure in combination with the effort discounting task. This task has previously been used to dissociate between the effort and delay requirements embedded within the effort discounting task (Floresco et al, 2008b; Ghods-Sharifi et al, 2009; Ghods-Sharifi and Floresco, 2010). In this task, the effort requirement to obtain the LR/HR was identical to the standard task, but selection of the LR option incurred a delay to reward delivery comparable to the time required to complete the ratio of presses on the HR lever. Thus, this procedure effectively equalizes the relative delay costs associated with the HR and LR options. It follows that if the effects of stress on effort discounting are due to a reduced tolerance for delays to reward delivery associated with greater effort costs rather than the work requirements themselves, then stress would not be expected to affect choice under these conditions.

Methods

A group of 13 rats were trained on the effort discounting task using procedures identical to those used for Experiment 1. After 16 days of training on the standard effort-discounting task, they were then trained on a modified version of the original task. Here, a single press on the LR lever caused the immediate retraction of both levers and delivered 2 pellets after a
delay equivalent to that required for rats to complete the ratio of presses on the HR using the standard effort discounting procedure (0.7–12.5 sec). Thus, for each block of trials, the delay to reward delivery after an initial choice of either lever was equalized. The delay to receive two pellets after a single press on the LR lever increased across trial blocks and was calculated based on the average time it took rats to press the HR lever 2, 5, 10, and 20 times during the last 3 days of training on the effort-discounting task. For this experiment, the average delays were 0.7, 2.6, 6.1, and 12.5 sec in the first, second, third, and fourth trial block respectively. Thus, if rats required 12.5 sec to press the HR lever 20 times during the last trial block, a single press on the LR lever during this block would deliver two pellets after a 12.5 sec delay. During these trials, the houselight remained illuminate throughout the delay. Rats were trained on this task for 8 days, at which point, they displayed stable levels of choice for three consecutive days. On the following day, they were subjected to the baseline control test followed by a restraint stress challenge on the next day.

**Results**

Restraint stress induced a marked decrease in the preference to work harder for a larger reward when the delay to reward delivery was equalized between the two options. Choice data was analyzed with a three-way within subjects ANOVA, with Test Day (baseline, 1 hour restraint) and Trial Block as two within-subjects factors. This analysis revealed a significant effect of Test Day ($F_{1,12}=6.928, p=0.022$), but not a significant Test Day x Trial Block
Figure 4. Effort discounting with equivalent delays following acute restraint stress. Effects of acute restraint stress on effort-based decision making with equivalent delays. (A) The ordinate shows the percent choice of the HR and the abscissa indicates the four trial blocks with increasing effort ratio of the HR (top) and increasing delay to reward delivery of the LR (bottom). Acute restraint stress decreased the selection of the HR option even when the delays to the delivery of the LR were similar. (B) Response latencies across the four trial blocks. Acute restraint stress increased the latency to respond in the second and third trial block. (C) Acute restraint stress did not affect the rates of lever pressing. Stars identify significant main effect where $p<0.05$. 
interaction ($F_{3,36}=1.122$, n.s.). This decrease in choice of the HR was apparent in the first trial block and persisted for the duration of the session (Fig 4A).

Acute stress also increased response latency in a manner similar to that observed in Experiment 1. Analysis of these data revealed a significant Test Day x Trial Block interaction ($F_{3,36}=3.37$, $p=0.029$), although the main effect of Test Day was not significant ($F_{1,12}=2.625$, n.s.). Simple main effects analyses confirmed that after 1 hour of restraint, the response latency in the second and third trial blocks were significantly higher ($p<0.05$) than on baseline day (Fig 4B). In this experiment, acute stress reduced locomotor activity relative to baseline (baseline: 775 +/- 74, 1 hour: 589 +/- 46; $F_{1,12}=10.247$, $p<0.01$). However, stress again did not alter the average rates of lever pressing on the HR lever ($F_{1,12}=0.12$, n.s.; Fig 4C). Additionally, stress did not alter the number of trial omissions (baseline: 2.54 +/- 1.24, 1 hour: 4.7 +/- 2.30; $F_{1,12}=1.714$, n.s.). Collectively, these data show that 1 hour of restraint stress causes a substantial decrease in the preference for animals to work harder to obtain a larger reward even when the delays to reward delivery between the HR and the LR option are equalized.

**Experiment 4: The effect of acute stress on delay-discounting**

Experiment 3 confirmed that the effects of acute stress on effort-based decision making do not appear to be attributable to a reduced tolerance for delays to reward delivery that are intertwined with higher effort requirements associated with larger rewards. However, the possibility remains that acute stress may also affect other forms of cost/benefit decision making when animals choose between smaller, immediate rewards and larger delayed rewards. In Experiment 4, we assessed the effects of acute stress on delay-discounting, using well-established procedures that were similar to the effort discounting task in many respects.
Methods

A group of 8 rats received initial lever press training in a manner similar to that used in Experiment 1. After three days of retractable lever training, rats received one day of reward magnitude discrimination, where over 48 choice trials, they chose between an LR lever that delivered 1 pellet and an HR lever that delivered 4 pellets immediately after each press. Subsequently, they received daily training sessions on a delay-discounting task (Zeeb et al, 2010). Like the effort discounting procedure, this task consisted of 48 trials, divided into 4 trial blocks, where the first two trials of each block were forced choice trials and the remaining ten trials were free choice trials. The intertrial interval was 70 sec, and a session lasted 56 min. On each trial, a single press on the LR lever resulted in the retraction of both levers and the immediate delivery of 1 pellet, with the houselight remaining illuminated for an additional 4 sec, after which the chamber reverted to the intertrial state until the next trial. Selection of the HR lever also caused the retraction of both levers, and delivered 4 pellets after a delay that increased across the four trial blocks (0, 15, 30, and 45 sec). During the delay, the houselight was extinguished and was reilluminated during food delivery that occurred at the end of the delay. Rats were trained for 25 days, after which they displayed stable patterns of choice behaviour. They were subsequently subjected to a baseline session, followed by a 1 hour restraint stress challenge on the next day.

Results

Restraint stress did not alter delay discounting. Analysis of the choice data revealed no effect of Test Day (F_{1,7}=1.123 , n.s.) nor a Test Day x Trial Block interaction (F_{3,21}=1.456 , n.s.; Fig 5A). Interestingly, in this experiment, restraint stress did not alter the latencies to make a choice (all Fs<3.17, n.s.; Fig 5B), nor did it affect locomotor activity (baseline: 1247 +/-110,
1 hour: 1119 +/- 115, F_{1,7}=1.69, n.s.). Furthermore, stress did not alter the number of trial omissions (baseline: 1 +/- 0.27, 1 hour: 0.625, +/-0.18, F_{1,7}=1.615, n.s.) These data suggest that in contrast to the effects of restraint on effort-related decisions, acute stress does not appear to reduce preference for larger, delayed rewards.

Figure 5. Delay-discounting following acute restraint stress. Effects of acute restraint stress on delay-discounting. (A) The ordinate shows the percent choice of the HR lever and the abscissa indicates the delays to HR delivery across the different trial blocks. Acute restraint stress did not alter the choice of the delayed HR. (B) Response latency across the four trial blocks. Acute restraint stress did not alter response latencies when choosing between a delayed HR and an immediate LR.

Experiment 5: The effect of acute stress on responding on a progressive ratio schedule of reinforcement

Experiment 2–4 confirmed that the effects of acute stress on effort-based decision making do not appear to be due to a fundamental disruption in motivation for objectively larger versus smaller rewards or a reduced tolerance for delayed rewards. However, the possibility remains that acute stress may disrupt other aspects of motivation which may in turn interfere with effort-related judgments. For example, acute stress may render animals either unwilling or
unable to respond on a lever repeatedly to obtain a reward. This possibility was assessed using a progressive ratio schedule of reinforcement, which is a well-established procedure for assessing motivation in rodents. If acute restraint stress decreases the motivation or the capability to press a lever repeatedly to obtain a food reward, then this manipulation would be expected to reduce instrumental responding under these conditions.

**Methods**

Thirteen rats were trained on a progressive ratio schedule of reinforcement. In this experiment, only the left lever was inserted into the chamber and remained in place for the duration of each training session. During the initial phase of training, rats learned over 30 min sessions to press the lever, using a FR-1 schedule of reinforcement on the first day, an FR-2 on the second day, and then two days of training using an FR-5 schedule. Completion of a ratio delivered a single reward pellet. They were then trained on a progressive ratio schedule, in which the ratio of presses required to obtain a single reward pellet increased after each pellet delivery. The ratio was adapted from the one used by Brown and colleagues (1998) and increased in the following manner: 1, 2, 4, 6, 9, 12, 15, 20, 25, 32, 40, 50, 62, 77, 95, 118, 145, 178, 219, 268, 328, 402, 492, 693, 737 and 901 presses. Rats had a maximum of 20 min to complete a ratio and obtain reward. Failure to complete a ratio in the allotted time ended the session and the animals were returned to their homecage until the next training day. The primary variables of interest were 1) the total number of lever presses made over the course of a session and 2) the total number of rewards obtained before a session terminates (breakpoint). Training continued for 22 days, after which the group displayed stable levels of lever pressing and breakpoints for three consecutive days (i.e.; less than 15%
variation within the group). They were then subjected to a baseline session and then a 1 hour restraint stress challenge.

**Results**

Acute stress did not alter responding on a progressive ratio of reinforcement. Analysis of the total number of lever presses made and breakpoints reached revealed no significant differences on these measures on baseline versus stress test days (total lever presses: $F_{1,12}=0.851$, n.s.; breakpoints: $F_{1,12}=0.144$, n.s.; Fig 6A, B). There was a small albeit non-significant decrease in overall locomotion, as indexed by the number of photobeam breaks/min (baseline; 22.02 +/- 2.33; stress; 18.803 +/- 1.92; $F_{1,12}=3.853$, $p=0.07$). Rates of lever pressing on baseline and stress test days were also analyzed. On the stressor day, all rats successfully completed the first 8 ratio requirements; however the final breakpoint varied across rats. We calculated the average rates of lever pressing to obtain the first 7 and the final 2 pellets on baseline and stress test days. Stress did not alter rates of lever pressing relative to baseline, (main effect of test day; $F_{1,12}=1.905$, $p=0.193$, n.s.; Test Day x Pellet interaction $F_{8,96}=1.464$, n.s.; Fig 6C). These findings are consistent with the lever pressing and breakpoint data, in that they indicate that acute restraint stress does not appear to reduce measures of motivation to work for food reward. Collectively, the results of this experiment in combination with those of Experiments 1-4 reveal that acute stress decreases the preference to work harder for a larger reward, but this effect is not due to a 1) disruption in preference for larger versus smaller rewards, 2) reduced tolerance towards delays, or 3) more fundamental disruptions in motivation to work for food reward.
Figure 6. Progressive ratio schedule of reinforcement following acute restraint stress. Responding on a progressive ratio schedule of reinforcement following acute restraint stress. Acute restraint stress did not alter the total number of lever presses (A) or the breakpoint (ie: total number of pellets) (B) relative to baseline. Acute restraint stress did not alter rates of lever pressing (C). Graph depicts rates of lever pressing to obtain the first 7 and last 2 pellets.
Experiment 6: The role of corticosterone in mediating the effects of acute stress on effort-based decision making.

Experiments 1-5 were designed to clarify the effects of acute stress on effort based decision making, and isolate some of the specific cognitive/motivational processes that may be affected by stress that leads to a reduced preference to work harder for larger rewards. Stress activates the hypothalamic-pituitary-adrenal axis, which increases the release of CORT (Tsigos & Chrousos, 2002). A subsequent experiment investigated whether administration of CORT could alter effort discounting in a manner similar to acute restraint stress. If the stress-induced reductions in preference for the high effort/HR option are mediated by increased CORT release, then injections of exogenous CORT would be expected to mimic the effects of acute stress on effort-based decision making.

Methods

A group of 12 rats were trained on the effort discounting task in a manner identical to Experiment 1. After 30 days of training, they displayed stable baseline levels of choice behaviour for at least three consecutive days. They were then subjected to the first of two injection test days. Each test day was part of a two day sequence. On the first day, all rats received a control vehicle injection (50/50 propylene glycol/0.9% saline, s.c.). After injections, rats were returned to their homecage and left undisturbed for 90 min, after which they were placed in operant chambers and received a training session. On the subsequent day, rats were split into two groups and matched for choice behaviour after vehicle injections, and then received their first counterbalanced injection of CORT (Sigma Aldrich). For this first test, half of the rats received a 1 mg/kg dose, and the other half a 3 mg/kg dose. After this first test day sequence, rats were retrained for 4 days until they again displayed stable
baseline levels of choice. They then received a second injection test day sequence (i.e.; vehicle injection on the first day, and a counterbalanced injection of either 1 or 3 mg/kg CORT on the second day). The behavioural parameters of interest did not differ between the first and second vehicle injections (all Fs<1.9, n.s.). Thus the average values of these measures were used for the data analysis. The doses of CORT used and the time course of administration have been shown previously to approximate increases in CORT release that occur during comparable durations of restraint stress (Meaney et al, 1988).

Results

Choice data were analyzed using a three-way between/within subjects ANOVA, with Order of treatment (1 or 3 mg/kg CORT first) as a between-subjects factor and Dose (vehicle, 1 mg/kg and 3 mg/kg CORT) and Trial Block as two within-subjects factors. As displayed in Fig 7A, treatment with either dose of CORT did not alter preference for the HR lever relative to vehicle injections (main effect of Dose: F2,20=0.004, n.s.; Dose x Block interaction: F2,20=1.16, n.s.). There were also no effects of Order of treatment or interactions with the within-subjects factors (all Fs<1.74, n.s.). Similarly, there were no effects of CORT on choice latencies (Fig 7B), rates of lever pressing (Fig 7C), trial omissions (vehicle: 0.17 +/- 0.11, 1 mg/kg: 0.25 +/-0.13, 3 mg/kg: 0.33 +/-0.14) or locomotion (vehicle: 747 +/-75, 1 mg/kg: 765 +/-85, 3 mg/kg: 734 +/-75; all Fs < 1.5, n.s.). These results indicate that administration of exogenous CORT does not mimic the effects of acute restraint stress on effort discounting or other behavioural measures. This in turn suggests that the effects of stress on effort-based decision making may not be mediated solely by increased endogenous levels of CORT, and that other neurochemical changes evoked by stress may be causing these effects.
Figure 7. Effort discounting following glucocorticoid administration. Effects of exogenous CORT administration (1 mg/kg and 3 mg/kg) on effort-based decision making. (A) Choice behaviour following the administration of either dose of CORT was comparable to choice after vehicle injection. (B) Similarly, response latencies were not affected by exogenous CORT relative to vehicle treatment. (C) CORT treatment did not alter rates of lever pressing.
Experiment 7: The role of dopamine in mediating the effects of acute stress on effort-based decision making.

In addition to increasing exogenous glucocorticoid levels, acute stress also promotes the release of a number of neurotransmitters that may alter certain processes related to decision making and other aspects of behaviour. In particular, it is well-established that acute stress (including restraint) can increase dopamine release in forebrain regions such as the PFC and NAc (Roth et al, 1988; Abercrombie et al, 1989; Imperato et al, 1989; 1991; Davis et al, 1994; Finlay et al, 1995; Rougé-Pont et al, 1998). Notably, increasing endogenous release of DA with higher doses of drugs such as amphetamine alters effort-based decision making in a manner similar to that induced by acute restraint stress, decreasing preference for a high effort/HR option on an effort discounting task (Floresco et al, 2008b; Floresco & Whelan, 2009). Therefore, it is possible that the effects of acute stress on different behavioral parameters related to this form of decision making may be mediated by excessive increases in endogenous DA. To test this hypothesis directly, we assessed how treatment with a low dose of the broad-spectrum DA antagonist flupenthixol altered the effects of acute stress on effort-related choice and response latencies. If the effects of acute stress on effort-related choice and response latencies are caused by excessive increases in DA release, then the administration of a DA antagonist should attenuate these effects.

Methods

A group of 12 rats were trained on the effort discounting task in a manner identical to Experiment 1. After 40 days of training, they displayed stable baseline levels of choice behaviour for at least three consecutive days. They were then subjected to the first of four test days: 1) saline/no stress, 2) saline/stress, 3) flupenthixol/no stress, or 4)
flupenthixol/stress. Rats were split into four groups of three, with each group receiving the four tests in a counterbalanced order, using a quasi-Latin Square design. This was done to control for any potential habituation to the stressor that may have occurred following repeated exposure to restraint. With this design, none of the rats in any of the groups were subjected to restraint stress on consecutive test days. For example, rats first assigned to the saline/no stress condition subsequently received saline/stress on the second test day, followed by the flupenthixol/no stress condition on the third test day and so on (see Fig 8).

![Figure 8](image)

**Figure 8.** The quasi-Latin square design order of stress and drug treatment. Counterballancing orders for stress and drug treatment used in Experiment 7. Order of saline/flupenthixol (FLU) in combination with the no stress/stress treatment in four distinct groups. Each arrow represents 5-7 days of retraining in between treatments.

On the first test day, all animals were injected with either saline or a low dose of flupenthixol (0.25 mg/kg, I.P., Sigma Aldrich). Following the injection, animals were returned to their homecage and left undisturbed for 10 min, after which they were subjected to either 1 hour of restraint stress, or left undisturbed in their homecage in a room similar to the stress procedure room for 1 hour. Behavioral testing for each rat commenced 10 min after being removed from the restraint tube/control room. Each subsequent test day was administered when choice behavior of rats within a particular subgroup was stable for 2
consecutive days. For this particular experiment, rats required a minimum of 5 and a maximum of 8 days of retraining between test days.

**Results**

Choice data were analyzed with a four-way between/within subjects ANOVA, with Order as a between subjects factor, and Stress Condition (no stress and stress), Drug treatment (saline and flupenthixol) and Trial Block as two within-subjects factors. This analysis revealed a significant main effect of Stress ($F_{1,8}=5.40, p=0.049$; Fig 9A). This result indicates that across drug/saline treatment conditions, restraint stress decreased the preference to work harder for a larger reward, replicating the effects observed in Experiment 1. Importantly, there was no main effect of Drug ($F_{1,8}=0.800$, n.s.) on choice behaviour, indicating that this dose of flupenthixol, administered 1 hour before behavioural testing was insufficient to alter choice. Of particular note, the analysis did not yield significant Stress x Drug or Stress x Drug x Trial Block interaction (all Fs< 0.877, n.s.). Thus, there were no differential effects of acute stress on choice after saline or flupenthixol treatment. This is demonstrated in Figs 9B and C, which show that although 1 hour of restraint stress decreases the choice of the HR option, administration of flupenthixol prior to the stressor did not reverse these stress-induced effects on choice behaviour when compared to the saline/stress treatment. The analysis did yield a significant Drug x Order interaction ($F_{3,8}=4.01, p=0.05$). However, this effect was driven by one subgroup of rats that received saline/stress as their first treatment. These rats showed a considerable increase in choice of the HR option during the last two test days under flupenthixol (82 +/-9%), relative to the first two tests after saline treatment (55 +/-16%). None of the animals in the other subgroups showed a similar drift in choice behavior across test days. Moreover, there were no other main effects of Order or interactions
with the Stress or Trial Block factors (all Fs<0.991, n.s.), confirming that regardless of treatment order, the effects of acute stress on choice did not change with repeated testing.

Figure 9. Effort discounting following pre-stress flupenthixol administration. (A) Percent choice of the HR lever after baseline or restraint stress averaged across saline and flupenthixol (0.25 mg/kg) treatment. Stress significantly decreased the selection of the HR options. The effect of (B) saline and (C) flupenthixol treatment, prior to restraint stress on effort discounting. Rats displayed a comparable stress-induced decrease in choice of the HR lever after saline and flupenthixol treatment, relative to injection days without stress. (D) Response latencies across the four trial blocks (left) and collapsed across blocks (right). Restraint stress preceded by saline injection caused a significant increase in choice latencies compared to saline alone. However, administration of flupenthixol prior to the stressor abolished this stress-induced increase in response latency. (E) There was no difference in the rate of lever pressing across the different experimental conditions. Stars identify significant main effect at p<0.05.
In contrast to the lack of effect of DA receptor blockade on stress-induced alterations in choice, flupenthixol did attenuate the effects of restraint on response latencies. Specifically, although there were no significant main effect of Drug or Stress (all Fs< 3.679, n.s.), the analysis did reveal a significant Drug x Stress (F_{1,11}=5.285, p=0.042) as well as a Drug x Stress x Trial block interaction (F_{3,33}=4.52, p=0.009). As shown in Fig 9D (right panel), acute stress after saline significantly (p<0.05) increased latencies to make a choice relative to saline alone. In addition, the enhanced latency observed after saline/stress treatment was significantly higher (p<0.05) than that observed following flupenthixol/stress. Moreover, response latencies following flupenthixol/stress treatment did not differ from those observed after flupenthixol alone (which also did not differ from saline alone). Subsequent simple main effects analysis of the three-way interaction further revealed that the attenuation of stress-induced increases in response latencies by flupenthixol occurred most prominently in the last trial block (Fig 9D, left panel). Rate of lever pressing did not differ across the four treatment conditions (all Fs < 1.42, n.s.; Fig 9E). Stress did not alter the number of trial omissions (saline/no stress: 0.083 +/-0.083; saline/stress: 0.33, +/-0.19; flupenthixol/no stress: 1.08 +/-0.57; flupenthixol/stress: 1.75, +/-1.052; all Fs <0.294, n.s.). Similarly, locomotor activity also did not differ across treatments (saline/no stress: 865 +/-90; saline/stress: 798, +/-84; flupenthixol/no stress: 726 +/-82; flupenthixol/stress: 698, +/-105; all Fs <2.55, n.s.). Collectively, the results of this experiment show that blockade of DA receptors with flupenthixol prior to acute restraint 1) does not interfere with the ability of stress to disrupt effort-related choice but 2) can reverse the increased latencies to make a choice induced by stress. This in turn suggests that the effects of stress on deliberation times, but not on choice, are mediated in part by increases in dopamine transmission.
Discussion

The main findings of the present series of experiments is that decision making involving evaluation of the costs and benefits associated with different options that vary in terms of their effort costs and reward magnitudes is sensitive to acute stress. One hour of restraint stress induced a reliable and robust decrease in the preference for rats to work harder to obtain a larger reward, shifting their bias to smaller rewards associated with a more nominal effort cost. Acute stress also increased latencies to choose between these different options. These effects are not easily attributable to a reduced tolerance for delays to reward delivery embedded within higher effort requirements, decreases in preference for larger versus smaller rewards or more general disruption in motivational processes. These stress-induced alterations in decision making do not appear to be mediated by increases in endogenous glucocorticoid activity, as they were not mimicked by the administration of exogenous CORT. However, some (but not all) of the effects of stress on this form of decision making may be mediated by increased DA activity. Administration of a DA antagonist reversed the increased choice latencies induced by acute restraint stress, but did not affect the decreased preference to work harder for a larger reward.

1-Cognitive/motivational aspects of the stress-induced effects on effort-based decision making

The effect of stress on choice

In Experiment 1, 1 hour but not 20 min of restraint stress decreased the preference for rats to choose the HR lever associated with a higher effort cost. Therefore, acute stress causes a decrease in the selection of the more demanding effort option, and this in turn decreases the amount of reward obtained in a single session. There are a number of cognitive or
motivational processes that could be disrupted by acute stress exposure, which would in turn shift the preference away from the high effort/HR option. Stress may have decreased the normal preference for larger versus smaller rewards. Alternatively, stress-induced decreases in preference for the HR option may reflect a decreased tolerance for delays to receiving reward that are intertwined with high effort requirements (i.e.: increased impatience). On the other hand, increased discounting of the larger reward option after acute stress may have been the result of a decrease in more general motivational processes that enable a rat to respond on a lever at high ratios repeatedly. Experiments 2-5 were conducted to assess each of these hypotheses and provide additional insight into the psychological mechanisms through which stress alters effort-related judgments.

One major consequence of the hormonal changes associated with acute stress is alterations in metabolic processes. Thus, stress can suppress appetite and digestion, but it also appears to increase the intake of highly palatable food with high fat/sugar content (Adam & Epel, 2007). These effects of stress may interfere with the natural bias to choose options associated with more versus less food reward, which could in turn alter cost/benefit evaluations related to effort-based decision making. Furthermore, stress can cause impairments in spatial memory (Diamond & Rose, 1994; de Quervain et al, 1998; Kim et al, 2007), therefore disrupting the ability to discriminate between the two levers, which could be interpreted as a decrease in preference for larger rewards. We addressed these issues in Experiment 2, using a reward magnitude discrimination task. This procedure was similar to the effort discounting task, with the key exception that there was no additional cost associated with the larger four-pellet reward. Using this task, rats showed a very strong preference for the larger reward under control conditions (~90% across all trial blocks). Note
that the relative lack of discounting of the HR lever in this experiment resulted in animals obtaining considerably more food reward than rats trained on the effort discounting task. Nevertheless acute stress did not alter the selection of the HR option on this task. These findings therefore suggest that the effects of acute stress on effort discounting are not due to a decrease in the subjective value of objectively larger rewards, or a disruption in the ability to distinguish between larger versus smaller rewards or discriminate between different levers.

Choosing to exert greater effort to obtain a larger reward imposes a longer waiting period to obtain that reward than lower effort options. Thus, it was unclear whether the effects of acute stress on effort discounting were attributable specifically to a reduced preference to wait longer or work harder for the HR. We assessed this possibility in two ways, the first being the use of an effort discounting with equivalent delays procedure which has been used previously to dissociate between the effort and the delay components embedded within the effort-discounting task (Floresco et al, 2008b). In this task, the delay to the delivery of the HR is the time required by each rat to complete the ratio, while the delay to the delivery of the LR is the average time necessary to complete the ratio of presses on the HR lever within each particular trial block. Thus, the relative contribution of the delays to reward on decision making is effectively equalized across both options. If follows that if the effects of stress on effort discounting were attributable primarily to a reduced tolerance for delayed rewards, then imposing an equivalent delay to reward delivery across both options would be expected to diminish the stress-induced effects on effort discounting. However, after an acute stressor, animals again showed a shift away from the high effort/HR option, despite the similar delay associated with the LR reward delivery under these conditions. Therefore, the decrease in the selection of the HR option does not appear to be attributable to
the delay embedded with the larger work output, and is more likely due to the comparably higher work load associated with the greater reward.

While the above results rectify the choice preference between two delayed options with different effort requirements, the possibility remained that acute stress may also affect other forms of decision making related to choice between smaller immediate rewards and larger delayed rewards. The delay-discounting task used in Experiment 4 was designed to elucidate the effects of stress on choice behaviour when only HR is associated with a longer delay to reward delivery while the LR can be obtained immediately. A key difference between this task and effort discounting is that in the former no additional work is required to obtain the larger/delayed reward. In this experiment, restraint stress did not decrease the preference for a delayed larger reward, further supporting the idea that stress is selectively decreasing the preference to work harder and not to wait longer for a greater reward. It is important to note the average time required to complete 20 presses were substantially lower in the equivalent delay than in the delay-discounting schedule of reinforcement (12.5 versus 45 sec, respectively). While the 45 sec of delay to the HR delivery did not deter the rats from selecting this option (Experiment 4), after an acute stressor, the 12.5 sec of sustained/intermittent work in the last trial block biased the rats’ choice away from this selection (Experiment 3). The lack of effect of acute stress on delay-discounting further confirms that the stress-induced effects on effort-based decision making are not due to increased “impatience” for delayed rewards. In addition, these findings also suggest that acute stress does not uniformly interfere with all forms of cost/benefit decision making in the same manner, and instead exerts a more selective effect on evaluations related to effort expenditures.
In contrast to the results of Experiment 4, studies with humans suggest a link between stress and impulsivity. Giora (1987) found that when performing under the threat of either controllable (performance dependent) or uncontrollable (random) shock, subjects were less likely to evaluate all alternative options when responding on a computerized analogy test. Using temporal discounting as a measure of impulsivity, Diller and colleagues (2011) report that female participants with high heart rate reactivity to stress show a greater discounting of the delayed option. It has been argued that stress may lead to overestimated perception of the time associated with the delay, leading to decreases in the preference for the delayed reward (Wittman & Paulus, 2008). However, the fact remains that there are some key differences between temporal discounting tasks used in human and animal research. While the human subjects choose between two reward values hypothetically delivered within days or as late as a year, delay-discounting studies in rats requires them to choose between immediate or a delayed rewards obtainable over the course of the same training session. It is also unclear whether given real-life decisions about a delayed monetary reward, human subjects would employ decision criteria similar to those they have used during the laboratory task. The sensitivity of temporal discounting to stressful events may therefore be more contingent on long-term time perception and not a general intolerance towards delays.

**The effect of stress on food seeking motivation**

The subjective value assigned to a certain reward is dependent in part on the amount of work that the outcome is *worth*, and hence that perceived value drives the motivation to work towards obtaining it. The findings of Experiments 1-4 suggest that acute stress decreases the preference to work harder for a larger reward, and that this effect is not a reflection of either intolerance towards delays, or a decrease in the subjective preference for larger rewards. One
other possibility is that stress may have caused a more general deficit in the motivation to work for food, or somehow interfered with their ability to respond on a lever at high ratios. This possibility was assessed using a progressive ratio task, which is a common manner to assess general motivation or the perceived worth of a fixed reward value. In the progressive ratio schedule of reinforcement, the associated cost of a certain reward increased with every single reinforcement, manipulating the relative value of a single food pellet. A key distinction between this experiment and the previous ones is that while the other tasks explicitly assessed choice behaviour between two similar yet distinct options, the progressive ratio task did not. Instead, this task simply measured the willingness to press a lever multiple times and with an increasing effort component for a single reward pellet in the absence of an alternative. As such, the “choice” rats made in this task was whether to work to obtain a reward or not.

Acute stress did not alter responding using progressive ratio schedule of reinforcement, as 1 hour restraint stress did not decrease the total number of lever presses in a single session breakthroughs (i.e.: the last ratio obtained) or rates of lever pressing. In this particular experiment, animals on average obtained 13-14 pellets, which correspond to 62 and 77 presses per pellet. In comparison, in the effort-based decision making task, rats could obtain four reward pellets after 20 presses on the HR lever in the last trial block, whereas the same number of presses in the progressive ratio task corresponds with the eighth single reward pellet. The fact that restraint stress did not interfere with the ability to maintain responding at considerably higher ratios to obtain less food than in the effort discounting study indicates that this manipulation does not render animals incapable of completing the required number of presses, nor is it decreasing their motivation to work for food
reinforcement. This result is also in keeping with the observations that restraint stress did not alter rates of pressing on the HR lever in Experiments 1 and 3. More generally, the results of Experiment 5 suggest that acute stress does not decrease the perceived worth of a reward. These results are in keeping with the findings of Schweimer and Hauber (2005), who proposed that there exist distinct regulatory pathways between choosing and accepting to work more to obtain food reinforcement. The findings of Experiment 5 are similar to a previous study demonstrating that exposure to chronic mild stress does not alter performance on progressive ratio schedule of reinforcement for a sucrose solution (Barr & Phillips, 1998). The results of the current experiment expand on these findings and confirm that a single exposure to an acute stressor does not alter instrumental responding for food on a progressive ratio schedule. Viewed collectively, this latter finding suggests that the decrease in the choice of the HR option observed in Experiment 1 is not due to stress-induced decreases in overall motivation, but instead may be more driven by the option to switch to a less demanding task.

In the absence of a choice between different options, acute stress does not simply decrease the effort “currency” an animal is willing to spend for a set reward. Rather, an acute stressor causes rats to opt for the choice that requires less work in exchange for less food. As such, it appears that acute stress shifts the decision criteria, whereby the relative, rather than absolute effort costs associated with larger rewards become less favored.

The alteration in effort discounting induced by restraint in rodents can provide novel insight that may increase our understanding of the manner in which decision making may be influenced after acute stress. As discussed earlier, stress alters decision making by increasing the likelihood of habitual behaviour in rats (Elliott & Packard, 2008) as well as promoting riskier but potentially more disadvantageous courses of action in humans (Miu et al, 2008;
Porcelli & Delgado, 2009; Putman et al, 2010; Diller et al, 2011). The results of Experiments 1-5 are in keeping with these findings from human studies, showing that effort judgments following a stressor are biased towards the less strenuous course of action, which actually reduces the amount of food reward that may be obtained in the long-term. Opting for the choice with relatively less effort requirement, the animal is guaranteed to receive less of the same palatable reward in addition to conserving the required energy to complete the high effort ratio. However, because this alteration in choice behaviour leads to greater energy conservation, this supposed suboptimal decision making pattern may not be completely disadvantageous. Therefore, these results support the notion that stress affects effort-based decision making by changing the response priorities when facing options with distinct effort demand, favoring those which require less energy expenditure.

**The effect of stress on choice latency**

In addition to shifting biases in choice behaviour, another effect of stress that was observed across numerous experiments was that it increased the deliberation time to choose between the two reward options. In Experiment 1, 1 hour restraint stress increased response latencies in the last 2 trial blocks, during which the effort requirements are 10 and 20 presses respectively. Similar effects of stress were observed on both the reward magnitude task (Experiment 2) and the effort discounting with equivalent delay procedure (Experiment 3). This increase in deliberation time after an acute stress suggest that the effect of this manipulation on choice does not appear to be the result of increased impulsivity, (ie; rats quickly choosing the LR option when faced with a choice). Furthermore, the fact that increases in response latencies were apparent as early as the second trial block argues against the interpretation that these effects reflect some form of satiety-induced hesitation. Note that
in some of these experiments, acute stress also tended to decrease locomotion, which may partially explain the increase in deliberation latency. For example, rats may have been slower to relocate towards the levers at the beginning of each trial. However, the fact that some experiments (2 and 7) yielded stress-induced increase in response latencies without affecting locomotion suggest that this explanation cannot fully account for these effects. Moreover, the increase in deliberation time was not a reflection of general slowing down of behaviour. In Experiments 1 and 3, upon choosing the HR option, rats responded as robustly as when in the baseline or 20 min restraint stress conditions. Additionally, the effects of stress on deliberation time and choice selection could also be dissociated, as demonstrated in Experiment 2 where acute restraint increased response latencies without affecting preference for the HR.

Choice latencies were not affected by stress when rats chose between a large delayed and a small immediate reward (Experiment 4). This lack of effect could stem from procedural differences between the delay-discounting relative to the other three decision making tasks used. One such difference is the magnitude of reward discrepancy between the LR and HR used in the delay-discounting in comparison to the other 3 experiments: in this former, rats are selecting between 1 and 4 reward pellets as opposed to 2 and 4 pellets. The greater relative reward gain that could be obtained in the delay-discounting experiment may have offset the effects of acute stress on choice latency. In addition, the intertrial interval used for the delay-discounting task was substantially longer than in the other choice tasks used (70 sec versus 40 sec). This longer intertrial interval may have led to greater anticipation for the subsequent trial, making rats less susceptible to the effects of stress on choice latencies. Despite this one result, acute restraint was effective at increasing choice
latencies in all of the other experiments of this study, suggesting that at least under some circumstances, stress increases hesitation to choose between options that differ in terms of reward magnitude and their relative effort costs.

The effects of restraint on choice latencies observed here are consistent with other reports showing increased response times following acute stress. Thermal stress has been shown to cause reversible increases in response latencies during performance of an avoidance-escape task (Weiss & Glazer, 1975) and attack-initiation behaviour (Corum & Thurmond, 1977). In these studies, the animals were slower to initiate avoidance-seeking behaviour, suggesting that the stress-induced increased latency is not limited to selection-related actions. It is therefore possible that stress increases the latencies to initiate a number of behaviours that demand the animal to become interactive and engaged with the environment. Collectively, these findings show that in addition to shifting decision biases away from larger rewards associated with a greater effort cost, hormonal/neurochemical changes occurring in response to acute stress also increase the processing times animals require to make these decisions.

2-Mechanisms of stress-induced effects on effort-based decision making

Experiments 1-5 explored the cognitive/motivational effects of stress to clarify the psychological mechanisms underlying its effects on effort-based decision making. Subsequent experiments investigated some of the hormonal and neuronal mechanisms underlying the stress-induced alterations in effort-related judgment. It is well-established that the initial activation of the hypothalamic-pituitary-adrenal axis by an acute stressor triggers the up and down regulation of a number of neuroendocrine functions, the most prominent being the release of glucocorticoids (Tsigos & Chrousos, 2002). Furthermore, neurochemical
studies have further confirmed that acute stress induces the release of DA in the forebrain and mesolimbic structures (Roth et al, 1988; Abercrombie et al, 1989; Imperato et al, 1989; 1991; Davis et al, 1994; Finlay et al, 1995; Rougé-Pont et al, 1998; Tsigos & Chrousos, 2002). Accordingly, we explored whether exogenous CORT administration would mimic the effect of acute restraint stress on effort-based decision making. In addition, we examined the potential contribution of increased DA receptor activity on the stress-induced alterations in behaviours associated with decision making.

The effect of exogenous glucocorticoid administration

Previous studies have shown that an acute exposure to restraint stress triggers the release of CORT (Kant et al, 1983; 1987; Meaney et al, 1988). To mimic this aspect of the stress response, we administered concentrations of exogenous CORT that would result in plasma levels of this hormone comparable to those obtained after similar periods of restraint (Meaney et al, 1988; Imperato et al, 1991). In contrast to the effects of acute restraint stress on effort-based decision making, treatment with 1 or 3 mg/kg CORT did not affect choice behaviour. Similarly, other behavioral measures (locomotion, rates of lever pressing and response latency) also remained unaffected after exogenous CORT. However, these results do not completely rule out the role of CORT in mediating the effects of stress on effort judgments. The possibility remains that relative changes in plasma CORT levels must precede other stress induced hormonal and neurochemical fluctuations, which in turn exert their effect on effort-based decision making. One way to address this issue in future studies would be to administer a glucocorticoid receptor antagonist prior to stress manipulations in an attempt to block stress-induced changes in decision making. Nevertheless, these results suggest that in the absence of a physical/psychological stressor, manipulating glucocorticoid
levels within the scope of this experiment did not affect choice or other behavioral measures associated with effort judgments. Therefore, the effects of acute restraint stress on this form of decision making do not appear to be solely the result of increases in plasma glucocorticoid levels.

The present findings contrast with those of other studies in animals and humans demonstrating that administration of exogenous CORT does induce alterations in learning and cognition that resemble those caused by acute stress. Administration of CORT in rats with doses comparable to ones used in the present study (1-5 mg/kg) has been shown to mimic the effects of acute stress on various cognitive functions such as contextual fear conditioning (Cordero & Sandi, 1998) and spatial memory retrieval (de Quervain et al, 1998) by enhancing and impairing performance on these tasks respectively. In humans, manipulations of cortisol levels through the administration of cortisol or dexamethasone can also alter both simple and more complex forms of cognition, such as declarative memory (Newcomer et al, 1994) and cost/benefit decision making (Putman et al, 2010). Taken together, these previous studies in addition to the present data indicate that although the effects of acute stress on some forms of learning and cognition can be mimicked by increased plasma glucocorticoid levels, other forms of cost/benefit decision making related to effort judgments are relatively insensitive to exogenous administration of CORT.

Of course, there are a number of other hormonal and neurochemical changes induced by acute stress that may underlie the behavioural effects reported here, that could either work independently or in concert with the actions of CORT to affect these types of decisions that an injection of CORT alone cannot induce. In fact, recent studies have attempted to pharmacologically reproduce the stress response using more complex approaches. For
example, human and animal studies report using NE reuptake inhibitor reboxetine in addition to synthetic glucocorticoids as a model of pharmacological stress-induced negative bias (Kukolja et al, 2008; Enkel et al, 2010) and as a way of mimicking the stress-induced amygdala activation (Kukolja et al, 2008). Likewise, manipulations of NE levels in combination with increased CORT release may be necessary for the pharmacological induction of stress-induced choice biases. Therefore, there are a number of alternative means which can be used to mimic the effects of stress on effort-based decision making. Further exploration of these approaches will enhance our understanding of how stress alters choice behaviour.

**Contribution of dopaminergic activity to stress-induced alterations in decision making**

Much of the evidence in the literature suggests that stress induced impairments in processes such as spatial working memory are reversed by DA receptor blockade (Murphy et al, 1996a; 1996b; 1997; Arnsten & Goldman-Rakic, 1998; Arnsten et al, 2000). With respect to the present study, effort-based decision making appears to be sensitive to DA availability and release, whereby low mesolimbic DA levels (Salamone et al, 1991; Salamone, et al, 1997; Salamone et al, 2003; Salamone et al, 2005) as well as high overall DA levels (Floresco et al, 2008b) can decrease the preference to work harder for a larger reward on an effort judgment task. Given the aforementioned effects of stress on mesocortical DA release (Roth et al, 1988; Abercrombie et al, 1989; Imperato et al, 1989; 1991; Davis et al, 1994; Finlay et al, 1995; Rougé-Pont et al, 1998) Experiment 7 attempted to clarify whether the reported alterations in effort-related choice behaviour were a result of stress-induced DA increases.

In well-trained rats, we observed that treatment with flupenthixol in the absence of stress did not affect performance on the effort-discounting task relative to saline treatment.
alone. This confirms that administration of a relatively low dose (0.25 mg/kg) of this DA antagonist, one hour prior to testing does not alter choice behavior, even though higher doses of DA antagonist given shortly before testing can affect this form of decision making (Floresco et al, 2008b). Following restraint stress, rats again shifted preference away from the HR option, replicating the effects of Experiment 1 in a separate cohort of rats despite their different handling and training experiences and pre-stressor manipulations. However, the effect of stress on choice was not altered by DA receptor blockade. This key finding suggests that the effects of restraint on effort-based decision biases do not appear to be mediated by stress-induced increases in forebrain DA release. This is in contrast to previous work demonstrating that stress-induced impairments in other forms of cognition such as working memory do appear to be mediated by increased DA activity (Murphy et al, 1996a; 1996b). As such, the present results suggest that other neurochemical changes associated with the stress response, independent of DA, mediate the shift in bias away from higher effort options during cost/benefit decision making.

In contrast to the inability of flupenthixol to reduce the effects of stress on choice behavior, these treatments did counteract increases in latencies to make a choice following restraint. Thus, acute restraint stress after a saline injection caused a significant increase in response latencies, replicating findings from our previous experiments (1, 2, and 3). However, this stress-induced effect on deliberation time was reversed by pretreatment with a DA receptor antagonist, even though this dose of flupenthixol by itself did not have an effect on this measure. Taken together, the results of Experiment 7 suggest that separate stress-induced behavioural alterations related to decision making may be regulated differentially by the dopaminergic system. Although blocking DA activity during stress did not reverse its
effect on choice biases, these findings suggest that the ability of acute stress to increase hesitation before response selection may be mediated by stress-induced increases in DA release.

**Other potential mechanisms mediating the effect of acute stress on decision making**

Collectively, the results of Experiments 6 revealed that stress-induced alterations in effort related decision making could not be replicated by exogenous administration of CORT. Although this experiment did not isolate the specific hormonal/neural mechanism responsible for the effects of stress on effort judgments, follow-up studies can further our understanding beyond the effects of CORT on mediating these alterations in choice behaviour. In addition to the release of glucocorticoids from the adrenal glands, acute stress also triggers a number of upstream neurochemical changes in the brain that may underlie the effects reported here. For example, Birnbaum and colleagues (1999) have shown that the administration of a NE antagonist reversed the working memory impairments induced by a pharmacological stressor. Similarly, post-training intra-amygdala infusions of CRH mimic the effects of acute stress on the stress-associated behaviours and on avoidance learning (Liang & Lee, 1988). These studies suggest that the effects of acute stress on effort-based decision making may be the result of increased CRH and NE release, although this remains to be tested experimentally.

In Experiment 7, systemic administration of a DA antagonist reversed the effects of stress on response latency and not choice behaviour. However, it is possible that the effect of acute stress on choice may be mediated by regionally-specific increases in DA activity, rather than global increases in release. DA activity in both the PFC and NAc has been implicated in mediating effort-based decision making (Salamone et al, 1991; Cousin & Salamone, 1994; Schweimer & Hauber, 2005), although how increased DA activity within these regions may
affect this form of decision making has not been studied. It is well-established that DA levels in the NAc and PFC increase during periods of acute stress (Roth et al, 1988; Abercrombie et al, 1989; Imperato et al, 1989; 1991; Davis et al, 1994; Finlay et al, 1995; Rougé-Pont et al, 1998; Tsigos & Chrousos, 2002). Moreover, stress-induced NAc DA increase is regulated by the PFC. Deutch and colleagues (1990) report that DA depletion in the PFC enhances the stress-induced NAc DA release in response to a mild foot shock. The complexity of this circuitry that both regulates and is activated by the stress response as well as effort judgments leaves open the possibility that the combination of stress and task challenges may differentially affect DA release in these separate terminal brain regions. Systemic blockade of DA receptors may have occluded the differential, regionally-dependent effects of this monoamine on choice behaviour related to cost-benefit decision making. However, the fact remains that systemic flupenthixol administration did reverse the stress-induced increases in response latencies. The possibility therefore remains that stress-induced DA increases may be more behaviorally selective, primarily mediating the stress-induced “hesitation” (response latency) but not the ultimate choice selection process. Future studies examining the effects of local administration of DA agonists and antagonist on decision making under basal and stress conditions may help to clarify these issues.

Conclusions

In summary, these experiments suggest that acute stress interferes somewhat selectively with cost/benefit evaluations concerning rewards of different magnitudes and the relative effort costs associated with obtaining them. These effects do not appear to be attributable to increased impulsivity, or reductions in motivation to work for food rewards or for larger rewards in general, nor do they seem to be caused solely by increased CORT activity.
Increased DA activity associated with stress also does not seem to be solely responsible for alterations in choice behaviour induced by acute stress, but may contribute to increases in latencies to make a choice. Collectively, these studies complement a growing literature investigating how acute stress may alter different types of cognitive processes, showing here that stress may change the manner in which animals value larger rewards associated with greater effort costs. One byproduct of this effect would be to cause an organism to conserve the energy that would otherwise be spent on the higher effort requirement associated with the larger reward. This in turn emphasizes that the stress response would reinforce the selection of less physically demanding options, possibly in an attempt to increase energy conservation. Given that the stress response is an adaptive one, the selection of the low effort associated option may help to promote energy conservation for the time immediately following a stressor.

Negative affect and depressed mood are the most recognized phenotypes of depression. However, individuals with clinical diagnosis of depression also suffer from a number of energy related deficiencies, such as psychomotor retardation, psychomotor slowing, anergia, and fatigue (Tylee et al, 1999; Stahl et al, 2002). Given the intertwined relationship between stress and depression (Heit et al, 1997), this animal model of effort-based decision making and its sensitivity to the effects of stress can enhance our insight into some of the underlying behavioral symptoms associated with depression. As such, this approach may not only further our understanding of the neural circuitry/neurotransmitter systems associated with the stress-induced alterations in cost benefit decision making, but may also serve as a model for the anergia and motivational deficits associated with
depression. This in turn may prove particularly useful in the development of novel treatments for this aspect of the disorder.
References


