

Stress and Cognitive Flexibility: Cortisol Increases Are Associated with Enhanced Updating but Impaired Switching

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Abstract

■ Acute stress has frequently been shown to impair cognitive flexibility. Most studies have examined the effect of stress on cognitive flexibility by measuring how stress changes performance in paradigms that require participants to switch between different task demands. These processes typically implicate pFC function, a region known to be impaired by stress. However, cognitive flexibility is a multifaceted construct. Another dimension of flexibility, updating to incorporate relevant information, involves the dorsal striatum. Function in this region has been shown to be enhanced by stress. Using a within-subject design,

we tested whether updating flexibility in a DMS task would be enhanced by an acute stress manipulation (cold pressor task). Participants' cortisol response to stress positively correlated with a relative increase in accuracy on updating flexibility (compared with trials with no working memory interference). In contrast, in line with earlier studies, cortisol responses correlated with worse performance when switching between trials with different task demands. These results demonstrate that stress-related increases in cortisol are associated with both increases and decreases in cognitive flexibility, depending on task demands. ■

INTRODUCTION

Acute stress is pervasive and can profoundly influence cognitive functions. One critical function modulated by stress is cognitive flexibility, which, broadly speaking, refers to the ability to adapt behavior to situational demands. This dynamically trades off with cognitive stability or persisting with a set of behaviors. Although a prominent finding in the literature is that acute stress impairs cognitive flexibility (e.g., Plessow, Kiesel, & Kirschbaum, 2012; Nikiforuk & Popik, 2011; Liston et al., 2006), we sought to investigate whether there are circumstances under which stress can enhance this dimension of cognitive control.

In the laboratory, cognitive flexibility is often measured by having participants switch between strategies. For example, in the nonhuman animal studies, task switching has been assessed by presenting cues from different modalities (such as texture and odor) where only one modality was relevant at a given time. In a typical task (Birrell & Brown, 2000), rats were trained to dig in a particular pot to obtain a food reward. They needed to switch between attending to cues of one modality (e.g., choose the pot with a specific texture) to using the other (e.g., choose the pot with a specific odor) to

find the reward. Stress has been shown to impair performance on such extradimensional attention shifting tasks in rats (Nikiforuk & Popik, 2011, 2014; Butts, Floresco, & Phillips, 2013; Bondi, Rodriguez, Gould, Frazer, & Morilak, 2008; Liston et al., 2006). In analogous tasks in humans (e.g., requiring participants to switch between responding to the color and the motion of a grating), individuals with chronic stress (Liston, McEwen, & Casey, 2009) or posttraumatic stress disorder (Pang et al., 2014) showed impaired performance. Chronic (Orem, Petrac, & Bedwell, 2008) and acute (Plessow, Kiesel, et al., 2012) stress also worsened performance on tasks involving task shifting (e.g., switching between categorizing numbers as odd/even to greater/less than five).

The neural processes supporting these forms of cognitive flexibility provide insight into the detrimental effects of stress. Set and task shifting typically implicate the pFC (Hamilton & Brigman, 2015; Nikiforuk & Popik, 2014; Shiner et al., 2014; Armbruster, Ueltzhoffer, Basten, & Fiebach, 2012; Kehagia, Murray, & Robbins, 2010; Liston et al., 2006, 2009; Birrell & Brown, 2000; Rogers, Andrews, Grasby, Brooks, & Robbins, 2000). Acute stress has also been shown to impair other forms of cognitive flexibility thought to involve pFC function, such as dynamically changing levels of goal shielding or ignoring distractions (Plessow, Fischer, Kirschbaum, & Goschke, 2011; but see Plessow, Schade, Kirschbaum, & Fischer, 2012), solving anagrams, and generating compound remote associates (Alexander, Hillier, Smith, Tivarus, & Beversdorf, 2007).

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As stress has been shown to generally impair pFC function (Arnsten, 2009; Holmes & Wellman, 2009; Qin, Hermans, van Marle, Luo, & Fernandez, 2009), this suggests a mechanism by which stress could impair cognitive flexibility. Liston and colleagues directly tested this hypothesis, demonstrating that stress-induced decreases in dendritic arborization in the medial pFC predicted worse set shifting performance (Liston et al., 2006). However, it is worth noting that recent studies have failed to replicate the impairing effects of stress on task switching (George et al., 2015; Snyder, Hill-Smith, Lucki, & Valentino, 2015; Wingefeld, Wolf, Krieg, & Lautenbacher, 2011), emphasizing the need for continued investigation in this area.

As described above, a range of tasks, all implicating pFC function, have been used to measure the influence of stress on cognitive flexibility. However, cognitive flexibility is a multifaceted construct. One additional aspect of flexibility that is critical for adaptive behavior but has not been specifically assessed in earlier stress studies, is the ability to appropriately “gate” incoming information based on whether it is relevant to the task at hand (van Schouwenburg, den Ouden, & Cools, 2010; Hazy, Frank, & O’Reilly, 2006). The flexible component of this process allows new information in and uses it to update existing information. The opposite process—namely, to ignore new and maintain old information—provides an analogous metric of stability (Cools & D’Esposito, 2011). The influence of stress on the balance of these processes can have critical implications for daily functioning. Updating too readily can lead to increased distractibility, while being overly stable can result in rigidity and unresponsiveness. Furthermore, updating flexibility has a different neural architecture from the switching tasks described earlier. Working memory updating is related to dorsal striatal function (Fallon & Cools, 2014; Cools & D’Esposito, 2011; Dahlin, Neely, Larsson, Backman, & Nyberg, 2008; Hazy et al., 2006). The dorsal striatum (particularly dorso-medial) has been implicated in other dimensions of cognitive flexibility as well (Robertson, Hiebert, Seergobin, Owen, & MacDonald, 2015; Ali, Green, Kherif, Devlin, & Price, 2010; Ragozzino, 2007). Importantly, the role of the dorsal striatum in supporting these forms of flexibility leads to a different prediction about the effects of stress: whereas pFC function is often impaired by stress, dorsal striatum structure and function can be enhanced by stress (Delgado y Palacios, Verhoye, Henningsen, Wiborg, & Van der Linden, 2014; Packard, 2009; Quirarte et al., 2009; Cullinan, Herman, Battaglia, Akil, & Watson, 1995). Although fewer studies have examined stress and striatal function in humans, acute stress has been shown to lead to increased use of striatal learning strategies (Schwabe & Wolf, 2012), and physiological stressors in particular have been linked to increased dorsal striatal BOLD (Kogler et al., 2015). This suggests that, in these situations, stress could enhance cognitive flexibility.

In this study, we probe the effects of stress on this type of cognitive flexibility using a delayed match-to-sample

task (DMS). On some trials, participants are required to “update” the information they are holding in working memory (a form of flexibility eliciting dorsal striatal activity; Fallon & Cools, 2014). On other trials, participants need to “ignore” new information and maintain what they have already encoded (a form of stability associated with pFC activity; Fallon & Cools, 2014). Each participant performed the task twice: once after an acute stress manipulation and once after a control (nonarousing) manipulation. We hypothesized that stress-induced cortisol responses lead participants to perform better on trials requiring flexible updating and worse on trials requiring stability. In line with previous findings that stress impairs participants’ ability to switch between different task demands, we also hypothesized that stress would lead to worse performance when switching between trials of different types (e.g., switching from a flexible update to an ignore trial and vice versa).

METHODS

Participants

Thirty-eight participants (19 women; 18–30 years old; mean age = 23.37 years, $SD = 3.18$ years) completed the study for monetary compensation. Five additional participants were excluded because of inability to complete the stress manipulation ($n = 3$), insufficient saliva ($n = 1$), and a baseline cortisol level more than three standard deviations outside the mean ($n = 1$). All participants were fluent in English, had normal or corrected-to-normal vision, had normal color vision, and were not pregnant. To reduce factors that could interfere with the stress response, participants were excluded if they were taking antidepressants, antianxiety medications, beta blockers, or corticosteroids. One female participant reported taking an oral contraceptive. Participants provided written informed consent before participation. All procedures were approved by the New York University Committee on Activities Involving Human Subjects.

Procedure

The study was conducted using a within-subject design, in which one session included an acute stress manipulation (Cold Pressor Task, below) and one included a control condition. On average, the two sessions occurred 8.1 days apart ($SD = 3.6$ days, range = 5–21).

To control for circadian fluctuations in cortisol levels (Lupien, Maheu, Tu, Fiocco, & Schramek, 2007), all sessions were conducted between 12:00 and 6:00 pm. The protocol for each session is described in Figure 1. Each session began with a 10-min acclimation period, during which participants completed demographic questionnaires as well as the Perceived Stress Scale (PSS). Participants were randomly assigned to complete the stress ($n = 20$) or control session ($n = 18$) first. Each session

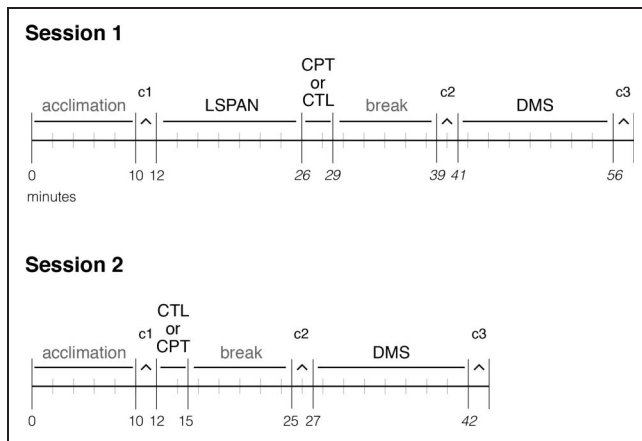


Figure 1. Experiment procedure. CTL = control condition; c1–c3 = cortisol measurements per session. Numbers in *italics* indicate average duration of task components across participants.

included three saliva samples to measure levels of cortisol. On the first day, participants completed the listening span (LSPAN) task. On both days, they completed the DMS task, which provided our measures of cognitive flexibility and stability.

Stress Manipulation and Validation

Cold Pressor Task

The cold pressor task (CPT) is a well-validated laboratory stress manipulation that has been shown to lead to increases in the stress hormone cortisol (Raio, Orederu, Palazzolo, Shurick, & Phelps, 2013; McRae et al., 2006; Lovallo, 1975). In the stress condition, participants submerged their nondominant arm in a bucket of ice water (mean temperature = 0.99°C, *SD* = 0.68°C) for three continuous minutes. The control condition followed the same procedure, but with warm water (mean = 38.6°C, *SD* = 0.85°C). The effectiveness of the stress manipulation was measured using salivary cortisol (below) and self-reported ratings of unpleasantness immediately after the water bath. Participants rated the experience on a scale from 0 (*not at all unpleasant*) to 10 (*extremely unpleasant*).

Cortisol Measurement

Three saliva samples were taken per session (Figure 1). These were used to measure levels of cortisol at baseline (c1), after the stress or control manipulation (c2), and after the DMS task (c3). All samples were stored in sterile tubes at –20°C. Samples were then shipped frozen to Salimetrics Testing Services (State College, PA). To derive a single measurement of cortisol in each session for statistical analysis (Δ Cortisol), cortisol values were log transformed, and the first timepoint in each session ($\log(c1)$; baseline) was subtracted from the mean of the second two timepoints (mean($\log(c2)$, $\log(c3)$); Otto,

Raio, Chiang, Phelps, & Daw, 2013). Averaging the last two timepoints provided an estimate of cortisol levels while participants were completing the DMS task.

Chronic Stress Levels

As recent work has demonstrated that prior experience of chronic stress is related to distinct effects of an acute stressor on set-shifting behavior (Snyder et al., 2015), we measured chronic stress levels in our participants. The PSS is a 10-item questionnaire that asks participants about their levels of stress during the past month (Cohen, Kamarck, & Mermelstein, 1983). For each item, participants rated how often they experienced each sensation (e.g., felt “upset because of something that happened unexpectedly”) on a scale from 0 (*never*) to 4 (*very often*). Stress levels were quantified as the sum of these ratings (reversed for reverse-coded questions) from participants’ first visit to the lab before any acute stress manipulation.

Working Memory Capacity

Participants completed an electronic version of the LSPAN task (Salthouse & Babcock, 1980), an index of working memory linked to dopamine synthesis capacity in the striatum (Landau, Lal, O’Neil, Baker, & Jagust, 2009; Cools, Gibbs, Miyakawa, Jagust, & D’Esposito, 2008). As previous work has shown that striatal dopamine increases following acute stress (Vaessen, Hernaus, Myin-Germeys, & van Amelsvoort, 2015; Abercrombie, Keefe, DiFrischia, & Zigmond, 1989), we wanted to test whether the effects of acute stress on updating flexibility (shown to involve the striatum) would vary based on baseline dopamine synthesis capacity.

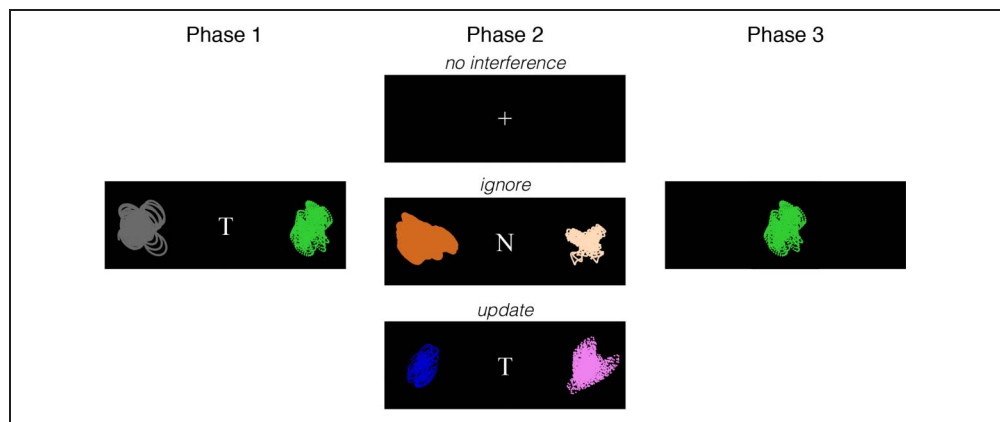
On each trial, participants listened to sentences and answered simple multiple-choice questions while remembering last word of each sentence they heard. The number of sentences on each trial (i.e., the span) increased from one sentence to seven sentences over the course of the task. Task performance was scored as described previously (Cools et al., 2008).

DMS Task

Participants completed 96 trials of a modified DMS task. Each session began with detailed instructions and an example trial completed with the experimenter. During the first session, participants completed 24 trials of practice.

Each trial consisted of three phases (Figure 2). First, two colored figures (computer generated “spirographs”) were presented on the screen along with the letter “T” (1 sec), followed by a blank ISI (2 sec). The second phase varied by trial type (presented for 1 sec). On No Interference trials, the second phase was a screen with a fixation cross; on Ignore trials, the second phase also had two colored figures with the letter “N,” indicating that these figures did not need to be remembered; and on

Figure 2. DMS task design. In Phase 1, participants encoded two colored figures. In Phase 2, they were required to either continue remembering these figures (no interference—no distraction; ignore—with distraction) or to forget those figures and remember two new colored figures (update). In Phase 3, they determined whether a presented probe figure matches one of the figures held in working memory.



Update trials, the second phase had two colored figures with the letter “T.” As with Phase 1, this was followed by a blank ISI (2 sec). During the third phase, a single colored figure was presented, and participants needed to determine whether it matched one of the figures previously presented with a letter “T” (2 sec). There were 32 trials of each type, randomly interleaved, over four blocks. As the trial types were randomly interleaved, an average of 29.6 trials (30.81%, range = 21.9–38.5%) of trials were preceded by another trial of the same type (“repeat” trials), whereas 65.4 (68.15%; 60.42–77.1%) were preceded by a trial of a different type (“switch” trials). On average, the task took 15.4 min to complete ($SD = 0.625$ min).

Data Analyses

To assess the effectiveness of the stress manipulation on physiological stress responses, we used repeated-measures ANOVA (rmANOVA) to assess the influence of stress session and time (both within subjects) on cortisol levels. We further validated these results with paired sample t tests comparing cortisol levels at each time point under Stress versus No Stress and, within the stress session, against baseline. For later analyses, cortisol levels were log-transformed and converted to a single cortisol response (Δ Cortisol) value per participant per session by log-transforming cortisol values, then subtracting the baseline value from the mean of the post-CPT timepoints (see Cortisol Measurement).

We first assessed the effect of stress on overall task performance by comparing accuracy between sessions using paired-samples t tests and using rmANOVA to examine performance across trial types within each session. We then ran an rmANOVA to target the effects of stress on performance across trial types, using Trial type and Stress session as within-subject factors. We expected that the magnitude of the physiological stress response (Δ Cortisol) would modulate stress-induced changes in performance and included the difference in Δ Cortisol between the Stress and No Stress session (continuous) as a covariate. To test whether effects of stress varied by sex (as reported by Espin et al., 2013; Guenzel,

Wolf, & Schwabe, 2013; Schoofs, Pabst, Brand, & Wolf, 2013; Andreano & Cahill, 2006; Jackson, Payne, Nadel, & Jacobs, 2006; and others), we also included Participant sex as a between-subjects factor. Additionally, we included chronic stress (PSS) and LSPAN in this analysis, and as we found no significant main effects or interactions, those analyses will not be discussed here.

To understand the results of the above rmANOVA, we correlated Δ Cortisol with accuracy on each trial type. To demonstrate that effects were specific to the acute stress manipulation, we focused on correlations between Δ Cortisol and accuracy within the Stress session, as well as the difference between Stress and No Stress sessions. Dependent correlations were compared using Steiger’s Z (Steiger, 1980). To test whether changes in flexibility during the stress session were driven by physiologically meaningful cortisol responses to the stressor, we compared performance under stress by “responders” (change in cortisol greater than 2.5 nmol/L, or 0.09 μ g/dL, from c1 to c2) and “nonresponders,” following criteria defined by Van Cauter and Refetoff (1985) (recently used by Radenbach et al., 2015).

Finally, to connect to previous literature on stress and task switching, we ran the same rmANOVA described above to assess the influence of stress on “switch” (trial immediately after a trial of a different type) compared with “repeat” (trial immediately after a trial of the same type) trials. For significant results, ANOVAs are supplemented with partial eta squared (η_p^2) and t tests with Cohen’s d (following Dunlap, Cortina, Vaslow, & Burke, 1996 for paired t tests) as effect size estimates.

RESULTS

Stress Response

We tested whether the CPT stress induction was effective by examining participant’s self-reported ratings of unpleasantness and salivary cortisol responses (Δ Cortisol). The stress induction was successful, leading to higher ratings of unpleasantness after the CPT (Stress session: mean = 8.45, No Stress session: mean = 0.63, $t(37) = 24.03$,

$p < .001$, $d = 3.9$) and robust increases in cortisol levels (Figure 3). Using an rmANOVA, with Condition (Stress vs. No Stress) and Time (baseline, 8 min postmanipulation, and after DMS task) as within-subject factors, we observed significant effects of Condition ($F(1, 37) = 25.81$, $p < .001$, $\eta_p^2 = 0.41$) and Time ($F(1, 37) = 13.05$, $p < .001$, $\eta_p^2 = 0.26$), and a Condition \times Time interaction ($F(2, 74) = 24.79$, $p < .001$, $\eta_p^2 = 0.40$). Whereas baseline cortisol levels did not differ between Stress and No Stress conditions ($t(37) = 0.6$, $p = .5$), cortisol levels were significantly higher in the Stress condition 10 min after the manipulation ($t(37) = 4.53$, $p < .001$, $d = 0.73$) and after the DMS task ($t(37) = 5.62$, $p < .001$, $d = 0.93$). In the Stress condition, cortisol levels increased significantly from baseline to 8 min after the stress manipulation ($t(37) = 4.78$, $p < .001$, $d = 0.77$) and after the DMS task ($t(37) = 4.97$, $p < .001$, $d = 0.81$). We computed Δ Cortisol as the mean level of cortisol during the DMS task after subtracting baseline cortisol levels (for details, see Methods). There was variability in how much participants reacted to the stress manipulation (mean Δ Cortisol during stress session = 0.57, range = -0.48 to 1.69). Levels of Δ Cortisol per participant did not differ based on whether the stress manipulation occurred during the first or second session ($t(36) = 1.22$, $p = .23$).

Stress and DMS Performance

Effects of Stress on Different Trial Types

We first tested whether there was an effect of stress on performance throughout the DMS task. Overall, stress did not significantly influence accuracy (Stress: mean = 90.73%; No Stress: mean = 91.47%; $t(37) = 0.83$, $p = .41$). We also did not observe significant differences in accuracy based on session order (Session 1: mean = 90.6%, Session 2: mean = 91.61%, $t(37) = -1.14$, $p = .26$).

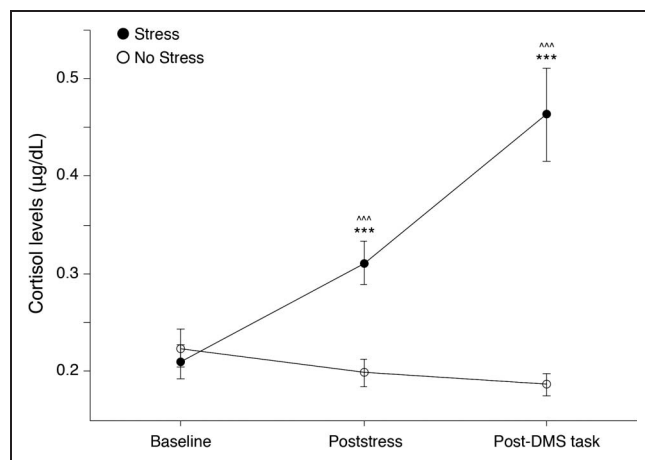


Figure 3. Cortisol levels per time point after CPT (Stress condition, filled circles) or control (No Stress condition, open circles). *** $p < .001$, Within Stress condition, comparing to baseline; ^^^ $p < .001$, Stress condition relative to No Stress condition per timepoint. Error bars = 1 SEM.

Our main hypothesis was that stress would have different effects on accuracy depending on the type of trial. To test this, we ran an rmANOVA with Trial type (Update, Ignore, or No Interference) and Session (Stress vs. No Stress) as within-subject factors and Difference in Δ Cortisol (between the Stress and No Stress sessions) and Sex as between-subject factors. Consistent with previous research (Fallon & Cools, 2014), we observed a main effect of Trial type ($F(2, 70) = 12.42$, $p < .001$, $\eta_p^2 = 0.26$). Across sessions, participants were more accurate on Update (95%) than Ignore (87.4%; $t(37) = 5.78$, $p < .001$, $d = 0.95$), Update than No Interference (90.9%; $t(37) = 5.45$, $p < .001$, $d = 0.88$), and No Interference than Ignore trials ($t(37) = 3.39$, $p = .002$, $d = 0.55$). Consistent with this, participants were also faster on Update (0.77 sec) than Ignore (0.81; $t(37) = 5.8$; $p < .001$, $d = 0.94$) and Update than No Interference (0.79; $t(37) = 3.59$, $p = .001$, $d = 0.58$). As we did not find any effects of our stress manipulation on RT (Table 1), all subsequent analyses focus on accuracy as a measure of performance.

Although we did not observe significant effects of Stress across the group (Stress \times Trial Type: $F(2, 70) = 1.66$, $p = .2$, $\eta_p^2 = 0.05$), there was large individual variability in the physiological response to the stress manipulation (Δ Cortisol range = -0.48 to 1.69). Supporting our hypothesis that the magnitude of the stress response would modulate stress-induced changes in performance, we found a significant Stress \times Trial Type \times Difference in Δ Cortisol interaction ($F(2, 70) = 3.37$, $p = .04$, $\eta_p^2 = 0.09$). To understand this interaction, we correlated Δ Cortisol with accuracy across trial types.

During the stress session, we observed a slight positive correlation between Δ Cortisol and accuracy on Update trials alone ($r(38) = .11$), this differed significantly from the negative correlation with No Interference trials ($r(38) = -.297$, $p = .07$; Steiger's $Z = 2.25$, $p = .025$). The smaller correlation with Update trial accuracy was likely due to a ceiling effect on Update trials (average accuracy in both sessions was approximately 95%; Table 1). When we correlated Δ Cortisol with the difference in accuracy on Update relative to No Interference trials, there was a significant positive correlation, such that higher Δ Cortisol correlated with better relative flexibility ($r(38) = .388$, $p = .016$). By contrast, Δ Cortisol had a slight negative correlation with accuracy on Ignore trials ($r(38) = -.16$), which did not differ significantly from the influence on No Interference trials ($Z = 1.09$, $p = .3$). The correlation between Δ Cortisol and accuracy on Update relative to Ignore trials was positive, but not significant ($r(38) = .238$, $p = .151$). Looking separately at cortisol "responders" and "nonresponders," we found a significant Trial Type \times Cortisol Responder interaction ($F(2, 72) = 4.31$, $p = .017$, $\eta_p^2 = 0.23$). Compared with nonresponders, responders showed significantly better performance on Update relative to No Interference trials ($t(36) = 3.12$, $p = .004$, $d = 1.09$) and Update relative to Ignore trials ($t(36) = 2.23$, $p = .03$, $d = 0.82$) during the stress session.

Table 1. Accuracy and RT per Trial Type during Stress and No Stress Sessions

| | Accuracy (%) | | RT (sec) | |
|---------------------------------|-----------------------------|-----------------------------|----------------------------|----------------------------|
| | Stress | No Stress | Stress | No Stress |
| <i>All Participants</i> | | | | |
| Update | 94.49 (5.31) ^{a,b} | 95.48 (4.91) ^{c,d} | 0.77 (0.13) ^{f,g} | 0.77 (0.14) ^{h,i} |
| No Interference | 90.13 (7.53) ^a | 91.69 (7.53) ^{c,e} | 0.79 (0.14) ^f | 0.79 (0.15) ^h |
| Ignore | 87.58 (9.71) ^b | 87.25 (9.81) ^{d,e} | 0.80 (0.12) ^g | 0.81 (0.13) ⁱ |
| Total | 90.73 (6.15) | 91.48 (5.97) | 0.79 (0.13) | 0.79 (0.14) |
| <i>Male Participants Only</i> | | | | |
| Update | 93.43 (4.81) | 94.57 (5.78) | 0.81 (0.12) | 0.79 (0.12) |
| No Interference | 89.31 (45.57) | 89.15 (8.16) | 0.82 (0.14) | 0.82 (0.13) |
| Ignore | 85.69 (9.45) | 83.06 (9.95) | 0.83 (0.12) | 0.85 (0.12) |
| Total | 89.15 (5.6) | 88.93 (6.2) | 0.82 (0.13) | 0.82 (0.12) |
| <i>Female Participants Only</i> | | | | |
| Update | 96.55 (5.09) | 96.38 (3.79) | 0.73 (0.13) | 0.74 (0.16) |
| No Interference | 90.95 (7.13) | 88.93 (6.19) | 0.76 (0.14) | 0.77 (0.17) |
| Ignore | 89.47 (9.84) | 91.45 (7.85) | 0.78 (0.12) | 0.77 (0.14) |
| Total | 92.33 (6.4) | 94.02 (4.6) | 0.76 (0.13) | 0.76 (0.16) |

Update vs. No Interference: ^a $p = .001$; ^c $p = .004$; ^f $p = .036$; ^h $p = .003$.

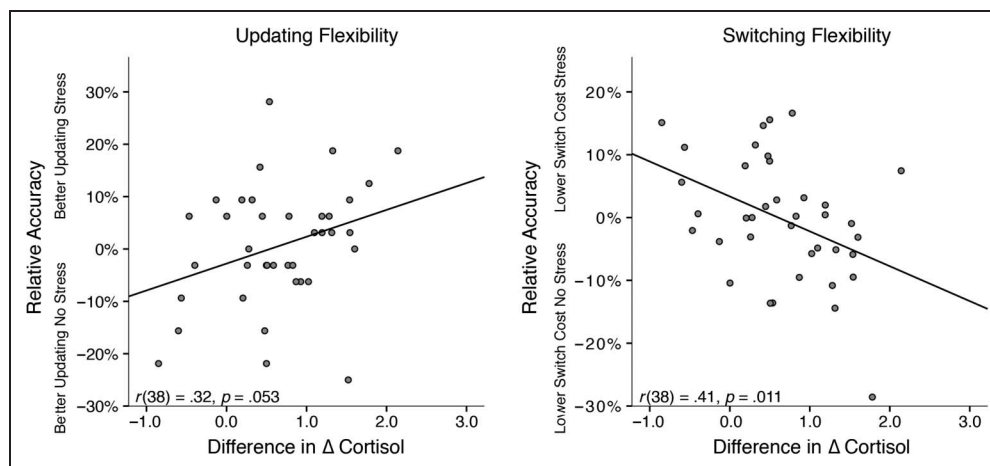
Update vs. Ignore: ^b $p < .001$; ^d $p < .001$; ^e $p = .001$; ⁱ $p < .001$.

Ignore vs. No Interference: ^c $p = .001$.

The relationship between Δ Cortisol and accuracy on Update relative to No Interference trials was specific to the acute stress manipulation. In the No Stress condition, there was no correlation between Δ Cortisol and Update relative to No Interference ($r(38) = .077$). Unlike the Stress condition, there was no significant difference between the correlation with Δ Cortisol and Update and the correlation

with Δ Cortisol and No Interference ($p = .6$). When considering the change in accuracy and change in Δ Cortisol between conditions (Stress–No Stress), there was also a trend toward a correlation between the difference in Δ Cortisol between sessions and change in relative Update accuracy (Figure 4; $r(38) = .317$, $p = .053$; when controlling for Sex in a partial correlation, $r(35) = .366$, $p = .026$).

Figure 4. Cortisol responses correlate with changes in flexibility. In both graphs, the cortisol response is quantified as the difference in Δ Cortisol between the Stress and No Stress sessions, and accuracy is computed as the difference between Stress and No Stress sessions. Left, cortisol response positively correlates with updating flexibility (difference in accuracy between Update and No Interference trials). Right, cortisol response negatively correlates with switching flexibility (difference in accuracy between “switch” and “repeat” trials).



Finally, performance varied by sex. We observed a main effect of Sex ($F(1, 36) = 6.44, p = .016, \eta_p^2 = 0.16$), with women having overall higher accuracy than men (Table 1; No Stress session: Women 94.02% [4.6%], Men 88.93% [6.2%]; $t(36) = 2.88, p = .007, d = 0.93$; Stress session: Women 92.33% [6.4%], Men 89.15% [5.6%]; $t(36) = 1.63, p = .112$). Although the correlations described above were consistent across male and female participants, on average, stress had different effects on accuracy based on trial type and sex (Stress \times Trial Type \times Sex: $F(2, 70) = 3.5, p = .036, \eta_p^2 = 0.09$). These variable stress effects were independent of the magnitude of Δ Cortisol, as male and female participants did not differ in stress response (no difference in Δ Cortisol during the Stress session: $t(36) = 0.69, p = .49$; no difference in change in Δ Cortisol between sessions: $t(36) = 0.82, p = .42$). Instead, we saw that stress overall had different effects on Update and Ignore trials (Stress \times Trial type [Update vs. Ignore] \times Sex: $F(1, 35) = 6.97, p = .012, \eta_p^2 = 0.17$). Although male participants on average showed improved performance on Ignore trials and impaired performance on Update trials after acute stress, female participants showed the opposite pattern (Figure 5, Table 1).

Effects of Stress on Switching between Trial Types

Previous research has demonstrated the negative effects of stress on task shifting (see Introduction). In the current experiment, participants completed trials with distinct tasks (e.g., they had to incorporate new infor-

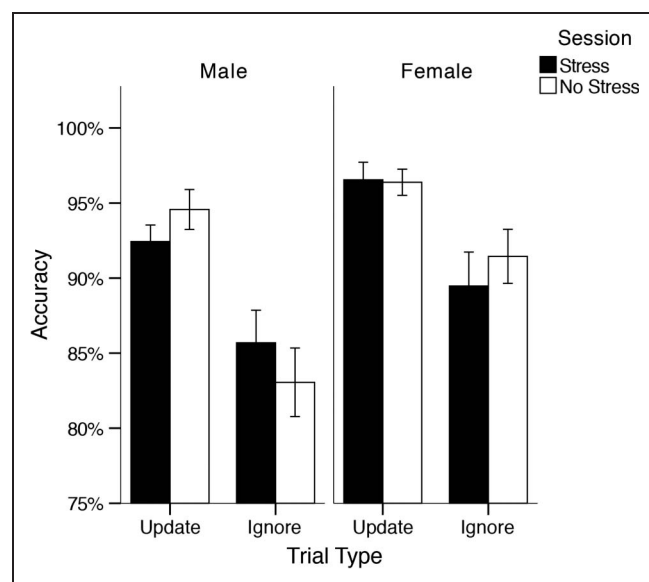


Figure 5. Change in performance after acute stress varies by sex. Accuracy on update and ignore trials during the DMS task are shown separately for male (left, $n = 19$) and female (right, $n = 19$) participants during stress (black bars) and no stress (white bars) sessions. There was a significant main effect of sex as well as a Stress \times Trial Type \times Sex interaction (see text for details).

mation or ignore distraction). As these trial types (“tasks”) were randomly interleaved, we examined whether stress also impaired accuracy when switching between different types of trials. To do this, we sorted trials based on what trial type immediately preceded it. If the two matched (i.e., there was no change in task), the trial was coded as “repeat”; if the two differed, it was coded as “switch.” We then subtracted accuracy during the No Stress condition from accuracy during the Stress condition to probe the influence of acute stress. To understand whether stress effects were influenced by the magnitude of the stress response, we correlated these changes in accuracy with changes in cortisol response between sessions.

Overall, stress impaired accuracy on “switch” relative to “repeat” trials (rmANOVA, Sex as between-subject factor: trend toward Stress Session \times Switch Type; $F(1, 35) = 2.997, p = .092, \eta_p^2 = 0.08$). As with updating flexibility, this relationship depended on the magnitude of the Cortisol response (Stress Session \times Switch Type \times Delta Cortisol; $F(1, 35) = 7.45, p = .01, \eta_p^2 = 0.18$). Thus, stress-induced increases in cortisol were associated with stress-induced increases in the switch cost ($r(38) = .41, p = .011$; Figure 4). Breakdown of this interaction showed that difference in Δ Cortisol trended toward correlating with worse performance on “switch” trials (Stress–No Stress: $r(38) = -.299, p = .068$; when controlling for sex in a partial correlation, $r(35) = -.333, p = .044$) and better performance on “repeat” trials (Stress–No Stress: $r(38) = .24, p = .1; Z = 2.51, p = .012$; Figure 5). When comparing cortisol responders and nonresponders, we found that responders showed significantly worse performance on “switch” trials during the Stress session ($t(36) = -2.66, p = .012, d = 0.995$). Finally, increased “switch” costs from the No Stress to the Stress session correlated with enhanced updating flexibility from the No Stress to Stress session, such that participants who showed better updating flexibility after stress also showed worse switching flexibility ($r(38) = .33, p = .043$).

As in the analysis above, there was a main effect of Sex ($F(1, 35) = 6.71, p = .014, \eta_p^2 = 0.16$), consistent with women having overall higher accuracy. However, unlike the earlier analysis, overall effects of stress on switching did not vary by sex (Stress Session \times Switch Type \times Sex: $F(1, 35) = 0.59, p = .45$).

DISCUSSION

In this study, we used a within-subject design to demonstrate conditions under which acute stress can enhance cognitive flexibility. Specifically, the process of working memory updating (shown to involve the striatum; Fallon & Cools, 2014) was enhanced by stress. Cortisol responses to acute stress positively correlated with better updating flexibility (i.e., greater accuracy on trials requiring updating relative to trials with no interference), but not with better stability (i.e., no correlation with accuracy on trials requiring participants to ignore distraction).

However, in line with previous work, larger cortisol responses to stress also related to greater switch costs (i.e., worse accuracy when changing between trials of different types).

The results showing that updating-based flexibility can be enhanced under stress stand in contrast to a large body of literature demonstrating that stress impairs cognitive flexibility (Nikiforuk & Popik, 2011, 2014; Pang et al., 2014; Butts et al., 2013; Plessow, Kiesel, et al., 2012; Liston et al., 2006, 2009; Bondi et al., 2008; Orem et al., 2008). However, as described earlier, the forms of flexibility involved in these earlier studies have been shown to critically involve the pFC (Hamilton & Brigman, 2015; Nikiforuk & Popik, 2014; Shiner et al., 2014; Armbruster et al., 2012; Kehagia et al., 2010; Liston et al., 2006, 2009; Birrell & Brown, 2000; Rogers et al., 2000), a region known to be impaired by stress (Arnsten, 2009). Although neuroimaging data are needed to understand the neural mechanisms by which stress influenced updating flexibility, previous work using this task has shown that updating flexibility involves the striatum (Fallon & Cools, 2014). Thus, it is possible that the different effects observed here are due to acute stress modulating striatal activity, in line with previous work showing that stress increases striatal dopamine levels (Vaessen et al., 2015; Abercrombie et al., 1989) and enhances striatal function in other cognitive domains (Leong & Packard, 2014; Schwabe & Wolf, 2012).

Our results demonstrate the importance of measuring physiological stress responses in determining the influence of acute stress on cognitive flexibility. For both updating flexibility and task switching, performance changes correlated with cortisol responses. Previous studies have shown that the magnitude of stress-induced cortisol correlated with reduced flexibility (Plessow et al., 2011) as well as changes in working memory performance (Schoofs, Wolf, & Smeets, 2009; Oei, Everaerd, Elzinga, van Well, & Bermond, 2006) and delayed recall (Elzinga, Bakker, & Bremner, 2005). Furthermore, the correlation between Δ Cortisol and updating flexibility in our study was specific to the stress manipulation, and participants classified as “cortisol responders” showed both better updating flexibility and worse switching flexibility under stress than “non-responders.” This raises the question of whether individual differences that underlie the magnitude of the stress response would explain distinct effects of stress on flexibility across participants. Although our cortisol measurements only provide an approximation of the stress response (by measuring pre- and posttask, our ability to detect peak cortisol responses in all participants is limited), these correlations highlight an important difference between stress-induced and stress-unrelated changes in cortisol. Unlike stress-induced changes in cortisol, stress-unrelated cortisol fluctuations (No Stress condition) were not sufficient to change flexibility.

Unlike previous studies (Plessow, Kiesel, et al., 2012; Plessow et al., 2011; Alexander et al., 2007), we did not observe an overall effect of the acute stress manipulation

on cognitive flexibility. These studies used a different stress manipulation, the Trier Social Stress Test (TSST). There are two important differences between the TSST and the CPT used in this study. First, socially evaluative stressors like the TSST have been shown to lead to post-task rumination (Zoccola, Dickerson, & Zaldivar, 2008), which has itself been linked to deficits in cognitive flexibility (Owens & Derakshan, 2013; Whitmer & Banich, 2007). Second, the TSST has been shown to lead to a greater increase in cortisol levels than the CPT (McRae et al., 2006). However, another study that administered high doses (120 mg) of hydrocortisone failed to find an effect on flexibility (Wingenfeld et al., 2011), suggesting that higher doses of cortisol alone are not sufficient to change flexibility.

Although exogenous cortisol administration leads to elevated levels of this hormone, an endogenous stressor (like the TSST or CPT) also evokes an adrenergic response. This adrenergic response has been shown to be associated with impaired pFC-dependent flexibility (Alexander et al., 2007; Beversdorf, Hughes, Steinberg, Lewis, & Heilman, 1999). Indeed this early wave of the stress response, which unfolds within seconds of the stressor (McEwen & Sapolsky, 1995), has been shown to strongly influence pFC function (Arnsten, 2009). In fact, in a previous study that found a group-level impairment of flexibility with stress, the cognitive flexibility task occurred during the stressor (a time at which adrenergic response is high) and was blocked by a β -adrenergic antagonist (Alexander et al., 2007). This adrenergic response was not measured in this study, although, as there was a 10-min delay between the stressor and the beginning of the flexibility task (chosen to maximize the cortisol response during the DMS task, as done by Raio et al., 2013), it is unlikely that this early wave of the stress response was directly influencing performance. Furthermore, previous research has shown that salivary α -amylase (an index of noradrenergic activity) did not significantly correlate with performance on a flexibility task at a similar delay, although salivary cortisol did (Plessow et al., 2011). However, in other cognitive domains, the interaction between the glucocorticoid and adrenergic system is critical for the effects of stress on behavior (e.g., Roozendaal, Okuda, Van der Zee, & McGaugh, 2006; Elzinga & Roelofs, 2005). Future research is needed to determine whether stress-induced cortisol responses interact with the early adrenergic response to change different forms of cognitive flexibility.

Despite not observing changes in updating flexibility as a result of the stress manipulation as a whole, we did see differences when looking at male and female participants separately. There was no difference between male and female participants in the effects of stress on switching flexibility, but effects of stress on updating flexibility did vary as a function of sex. From the No Stress to the Stress session, men became more accurate on Ignore trials and less accurate on Update trials, whereas

women showed the opposite pattern. As women were already highly accurate (96.4%) on Update trials without stress, the relatively small increase in accuracy after acute stress may be due to a ceiling effect. Nevertheless, both groups showed similar increases in cortisol (Δ Cortisol) in response to the acute stress manipulation, and for both groups, Δ Cortisol positively correlated with increased accuracy on Update relative to No Interference trials during the Stress session. Thus, regardless of sex, individuals with higher Δ Cortisol also showed better updating flexibility.

Different effects of stress on cognition for male and female participants have been reported in other domains, including long-term memory (Zoladz et al., 2014; Espin et al., 2013; Andreano & Cahill, 2006) and reversal learning (Laredo et al., 2015) as well as dopaminergic activity (Dalla et al., 2008). Some of these effects may be due to interactions between estrogen and cortisol (Ycaza Herrera & Mather, 2015). Our observation that men showed enhanced performance on Ignore trials during the Stress compared with the No Stress session is consistent with previous findings. During Ignore trials, participants needed to minimize interference from distracting images, and previous work has shown that stress attenuated distraction in men under conditions of low perceptual load (Sato, Takenaka, & Kawahara, 2012). Furthermore, our finding that stress had different effects on Update trial performance for men and women may be related to previous work showing that effects of stress on dorsal striatal function in other cognitive domains vary by sex. However, these findings are mixed. Although studies have shown stress-induced increases in BOLD response in the putamen in women (but not men; Wang et al., 2007) and stress-induced impairment in men (but not women) on a task thought to involve the dorsal striatum (stimulus–response memory; Guenzel et al., 2013), other work has shown that stress enhanced dorsal striatal BOLD in men but not women (Lighthall et al., 2012). Future research is needed to clarify the role of sex in the influence of stress on striatal function, and the circumstances under which stress may enhance striatum-dependent processes.

The current study contributes to a growing literature regarding the influence of acute stress on cognitive flexibility. By examining a distinct form of flexibility (namely, the ability to incorporate new information, rather than switching between task sets), this work highlights the multifaceted nature of this cognitive process. These results further demonstrate that this type of flexibility can be improved by the experience of acute stress.

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