

Stress increases behavioral resistance to extinction

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Received 14 December 2010; received in revised form 7 February 2011; accepted 7 February 2011

KEYWORDS

Stress;
Cortisol;
Memory;
Extinction;
Instrumental learning;
Habits

Summary Behavioral persistence is required to reach a goal but may impede adaptations to changing environments. Given the well-documented effects of stress on learning and memory processes, we asked here whether stress affects the persistence of behavior. Participants were exposed to stress or a control condition before they learned an instrumental action to gain a food reward. During learning, we presented several extinction blocks in which the food reward was not presented. Stress rendered participants' responding shortly after initial learning insensitive to the extinction procedure. Overall learning curves remained unaffected. Thus, the present findings suggest that stress increases the resistance of behavior to extinction. The cause of the behavioral persistence after stress may be its habitual form.

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1. Introduction

Habits and routines are woven into the fabric of our everyday lives. They are performed almost automatically, thus allowing attention to be focused elsewhere but reducing flexibility in the face of ever-changing environments (Graybiel, 2008). Habits develop over time, as a function of practice. During early stages of learning, actions are goal-directed; they are guided by the current incentive value of the goal in conjunction with knowledge of the causal relationship between action and goal. As learning proceeds, however, actions become more and more habitual, stimulus-driven, and independent of the action-outcome contingency (Dickinson,

1985; Balleine and Dickinson, 1998a). This shift is accompanied by a transition at the neural level from prefrontal cortical to dorsolateral striatal control over action (Balleine and Dickinson, 1998a; Yin et al., 2004; Valentin et al., 2007; Tricomi et al., 2009).

May other factors than training promote habit formation? It is well documented that stress and stress hormones, such as catecholamines and glucocorticoids (mainly cortisol in humans), influence learning and memory processes (for reviews de Quervain et al., 2009; Roozendaal et al., 2009; Schwabe et al., 2010a). Although previous research demonstrated mainly stress effects on hippocampus-dependent memory (de Quervain et al., 1998; Lupien et al., 1998; Buchanan et al., 2006; Payne et al., 2007; Schwabe et al., 2009), recent evidence shows that stress modulates striatum-dependent memory processes as well (Quirarte et al., 2009). Moreover, stress can turn instrumental responding insensitive to changes in the value of a goal (Dias-Ferreira et al., 2009; Schwabe and Wolf, 2009). In particular, we could show in a previous study that stress before learning renders participants' behavior insensitive to the devaluation of a goal

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(Schwabe and Wolf, 2009). In this study, however, the stress hormone cortisol, one of the key mediators of stress effects on memory processes, was elevated both before learning and before the critical test of the nature of instrumental responding. Thus, stress (hormones) could have affected the acquisition and the expression of habitual behavior. Whether stress may indeed affect the formation of habits remains still unknown.

The gold standard to examine habit behavior is the outcome-devaluation paradigm in which subjects are initially trained to perform a certain action to gain a particular reward (e.g. a particular food). Subsequently, this food is devalued (e.g. by feeding subjects to satiety with that food) before subjects perform the previously learned action in extinction. Goal-directed behavior is indicated by a decrease in responding to the devalued action. Habit behavior is indicated by the insensitivity of responding to the changes in the value of the goal (Balleine and Dickinson, 1998b). While goal-directed and habitual behavior can be elegantly distinguished with this procedure, changes of instrumental behavior across training can only be assessed in a between-subject design (e.g. Dickinson et al., 1995). In order to examine stress-induced changes in instrumental responding within a participant we used therefore a modified contingency degradation procedure (Balleine and Dickinson, 1998a). Participants were exposed to a stressor (Socially Evaluated Cold Pressor Test; Schwabe et al., 2008) or a control condition before they learned an instrumental action that yielded a food reward with a high probability. Across learning, we interspersed repeatedly blocks in which the reward was not presented (i.e., extinction blocks).

This experiment examined stress-induced changes in the sensitivity of instrumental action 'online', i.e., across the learning session. Based on previous evidence indicating that stress may promote habitual responding (Schwabe and Wolf, 2009), we hypothesized that stressed participants would become relatively shortly after initial learning insensitive to extinction.

2. Methods

2.1. Participants

Seventy-six healthy, normal-weighted students of the Ruhr-University Bochum (38 men, 38 women; age: $M = 24.0$ years, $SEM = 0.3$ years; body-mass index: $M = 22.6$ kg/m², $SEM = 0.3$ kg/m²) participated in this experiment. Exclusion criteria were checked in a standardized interview and comprised present or lifetime history of mental disorders, current treatment with psychotropic medications, narcotics, beta-blockers or steroids, drug abuse, any food intolerance, current or planned diet, smoking and in women the use of oral contraceptives. Furthermore, participants were pre-screened to ensure that they found the food rewards that were used in the experiment (chocolate milk, orange juice) pleasant. Nevertheless, we had to exclude 12 participants (6 men, 6 women) from further analyses because they revealed during the experiment that they did not like the reward (they rated the pleasantness of the reward below 20 and choose the reward-associated high-probability action in less than 25 percent of the trials, which corresponds to pleasantness ratings and percent of high-probability actions that were

at least two standard deviations below the referring means), thus leaving a sample of 64 participants.

Participants were asked to refrain from excessive exercise, caffeine and eating within the 3 h before testing. All participants provided written informed consent for their participation in the protocol as approved by the ethics committee of the German Psychological Society.

2.2. Procedure

To reduce the impact of diurnal variation in levels of the stress hormone cortisol, all testing took place between 1300 h and 1800 h. After their arrival at the laboratory, participants were randomly assigned to the stress or control condition (16 men and 16 women per group). In the stress condition, participants were exposed to the Socially Evaluated Cold Pressor Test (SECPT), as described in detail elsewhere (Schwabe et al., 2008). They were asked to immerse their right hand up to and including the wrist for 3 min (or until they could no longer tolerate it) in ice water (0–2 °C). During hand immersion they were monitored by an unfamiliar person and videotaped as social evaluation is critical for stress-induction (Dickerson and Kemeny, 2004). In the control condition, participants submerged their right hand up to and including the wrist for 3 min in warm water (35–37 °C); they were neither monitored nor videotaped.

In order to assess the efficacy of the stress manipulation, saliva samples were collected by means of Salivette[®] (Sarstedt, Germany) collection devices immediately before as well as 1 min, 25 min and 65 min after cessation of the SECPT or control manipulation. The concentrations of the stress hormone cortisol were measured from saliva using an immunoassay (IBL, Hamburg). Moreover, blood pressure measurements were taken immediately before, during and immediately after the SECPT or control manipulation with a Dinamap system (Critikon[®], Tampa, FL; cuff placed on the left upper arm) and subjects rated immediately after the SECPT or control manipulation on a scale from 0 ("not at all") to 100 ("very much") how stressful, painful and unpleasant they had experienced the previous situation.

Twenty-five minutes after the SECPT/control manipulation, participants rated their hunger and the pleasantness of the foods that were used in the learning task (chocolate milk/orange juice, peppermint tea, water) on a scale from 0 ("not at all") to 100 ("very much") and indicated whether they liked orange juice or chocolate milk best; the preferred food was used as reward. Afterwards, participants completed the instrumental learning task (Fig. 1). They were presented two different trial types: reward and neutral. On each trial, participants were asked to choose between two actions represented by two distinct symbols on the computer screen. After participants had selected one of the two actions by clicking with the mouse cursor on the referring symbol, this symbol was highlighted for 3 s and 1 ml of a liquid food or else no liquid was delivered, according to the reward schedule associated with the chosen action. The liquids were delivered with separate electronic pumps (one pump for each liquid) and transferred via 3 m long tubes (diameter: 3 mm) to the participants who kept the ends of the tubes between the lips. For both neutral and reward trials, there were reinforcement and extinction blocks.

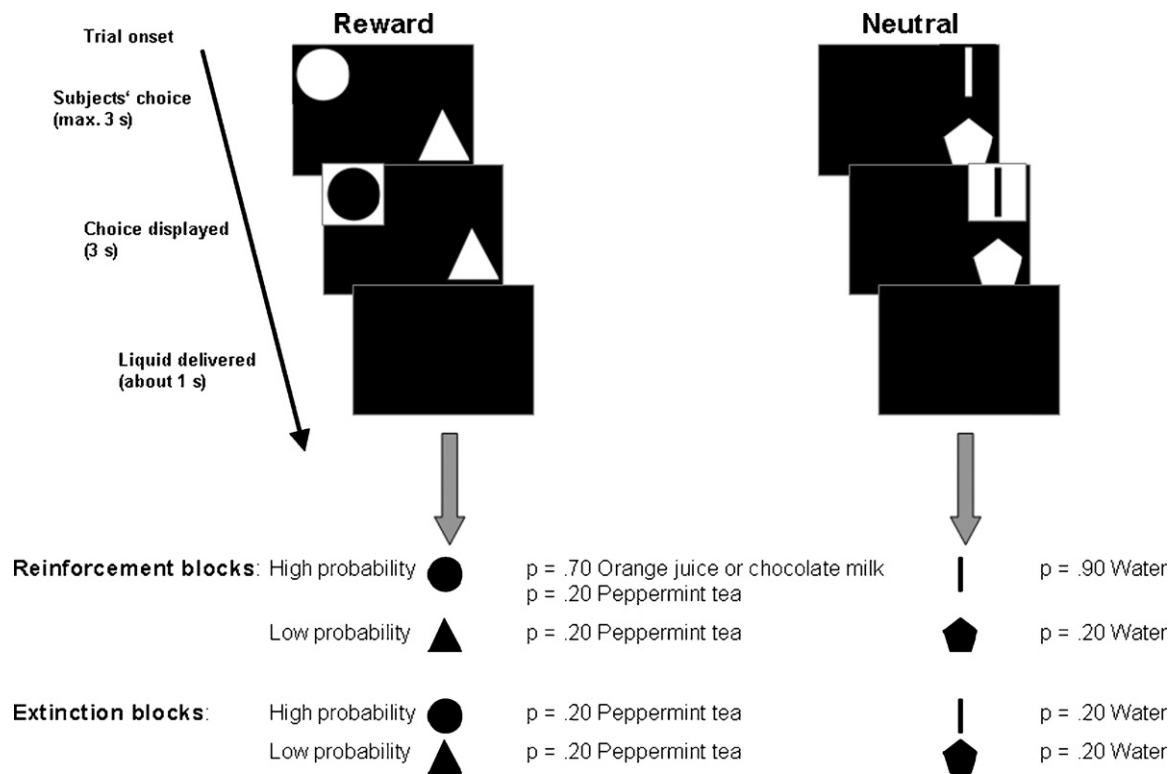


Figure 1 Illustration of the experimental paradigm. Participants completed two trial types: reward and neutral. On each trial, they were asked to choose between two actions represented by distinct symbols. In the reinforcement blocks, there was for each trial type one action that led with a high probability to a food outcome whereas the other led with a low probability to a food outcome: in the reward trials, the high-probability action delivered the reward (orange juice or chocolate milk, depending on participants' preferences) with a probability of .70 percent, a common liquid (peppermint tea) with a probability of .20 or else nothing; the low-probability action delivered the common outcome with a probability of .20 but never the reward. In the extinction blocks, participants received only the common outcome with a probability of .20, irrespective of the performed action. When an action was chosen the related symbol was highlighted for 3 s before the outcome was delivered. Parts of this figure are reproduced from Schwabe and Wolf (2009), with permission of the Society for Neuroscience.

In reinforcement blocks, the two actions per trial type differed in the probability with which a food outcome was delivered. While one action was followed with a probability of $p = .90$ by a food outcome (*high-probability action*), the probability of a food outcome was $p = .20$ for the other action (*low-probability action*). On reward trials, the high-probability action led to the reward (chocolate milk or orange juice depending on participants' preference) with a probability of $p = .70$ and to a common outcome (peppermint tea) with a probability of $p = .20$. The low-probability-action was never associated with the reward but led only to the common outcome with a probability of $p = .20$. On neutral trials, both actions were followed by water, either with a probability of $p = .90$ (high-probability action) or $p = .20$ (low-probability action). The neutral trials served as a control for the effect of the reward on participants' choice behavior.

In extinction blocks, the reward was never presented and the two actions per trial type were both associated with the same food outcome probabilities as the referring low-probability actions in the reinforcement blocks. The extinction block served to assess to what extent participants' instrumental behavior was guided by the action-outcome (i.e. the reward).

In total, participants were presented 160 reward and 160 neutral trials (duration: ~ 30 min). For each trial type, 20-trial reinforcement blocks alternated with 10-trial extinction blocks; the last extinction block was followed by another 10 extinction trials to assess the persistence of the learned actions. Note that the overall reward probability associated with the high-probability action was about 44 percent which is comparable to previous studies on goal-directed vs. habitual learning (Valentin et al., 2007; Schwabe and Wolf, 2009). The occurrence of the reward vs. neutral trials was fully randomized. The specific assignment of the symbols and the positions on the computer screen to each action was held constant for each subject but counterbalanced across participants.

Finally, participants rated again their hunger and the food pleasantness.

2.3. Statistical analysis

Salivary cortisol and blood pressure data were analyzed by separate group (stress vs. control) \times time point of measurement ANOVAs. Participants' responses in the reward and neutral trials were submitted to mixed-design ANOVAs with

the between-subjects factor group (stress vs. control) and the within-subject factors training block (first vs. second vs. third vs. fourth vs. fifth training block) and block type (last reinforcement block before extinction vs. extinction block). Significant three-way interactions were pursued by group \times block type ANOVAs for each training block. All reported p -values are two-tailed.

3. Results

3.1. Physiological and subjective stress responses

Endocrine, autonomic and subjective measurements verified the stress-induction by the Socially Evaluated Cold Pressor Test (SECPT). All but 5 participants (range: 57–115 s) of the stress group kept their hand for the full 3 min in the ice water. These 5 participants did not differ in their stress responses from the rest of the stress group.

3.1.1. Salivary cortisol

Salivary cortisol concentrations increased in response to the SECPT but not in response to the control condition (group \times time point of measurement interaction: $F(3, 159) = 12.43$, $p < .001$, $\eta^2 = .19$). As shown in Table 1, stressed participants had higher cortisol concentrations than control participants 25 min after the SECPT/control condition ($p = .001$), whereas groups were comparable before, immediately and 65 min after the treatment (all $p > .21$).

3.1.2. Blood pressure

The SECPT elicited significant elevations in systolic and diastolic blood pressure, while the control condition did not. As shown in Table 1, groups differed in systolic and diastolic

blood pressure during but neither before nor after the stress and control condition, respectively (group \times time interactions for systolic and diastolic blood pressure: both $F(2, 124) > 52$, both $p < 0.001$, both $\eta^2 > 0.46$).

3.1.3. Subjective assessments

As expected, participants that were exposed to the SECPT experienced the hand immersion as significantly more stressful, painful and unpleasant than participants of the control group (all $t(62) > 17$, all $p < .001$, see Table 1).

3.2. Instrumental learning

All participants, irrespective of the experimental group, increasingly favored the high-probability action associated with the reward over its low-probability counterpart. They preferred the reward-associated high-probability action from the first 10-trial block on (binomial test, all $p < .001$) indicating that they learned quickly which action was associated with the reward (Fig. 2A). On the contrary, participants did not chose the high-probability action associated with the neutral outcome more often than the referring low-probability action (all $p > .05$, Fig. 2B) suggesting that they were indifferent as to whether they received the effectively neutral control liquid (value \times block interaction: $F(15, 930) = 2.59$, $p < .01$, $\eta^2 = 0.04$; main effects for block and value: both $F > 3$, both $p < .01$, both $\eta^2 > 0.05$). Stress had no effect on participants' learning curves (main effect group and interactions involving the factor group: all $p > .26$).

In order to assess the influence of stress on the sensitivity of instrumental behavior to repeated extinction blocks, we compared participants' responses in reinforcement and extinction blocks across neutral and reward trials. For neutral trials, there were no significant main effects of training block, block type or group and no interaction between any of these factors (all $p > .25$) which suggests that all participants, irrespective of the treatment, were indifferent as to whether they received the effectively neutral outcome or not (Fig. 2). For reward trials, however, there was a strong trend for a three-way interaction between training block, block type, and group ($F(4, 248) = 2.00$, $p = .09$, $\eta^2 = 0.03$) indicating a differential effect of stress on instrumental responding in reinforcement and extinction blocks depending on the training block. Follow-up analyses showed that stress had a significant differential effect on behavior in reinforcement and extinction blocks in the second and fourth training block (block type \times group interactions: both $F(1, 62) > 3.95$, both $p < .05$, both $\eta^2 = 0.06$). As shown in Fig. 2, control but not stressed participants decreased responding to the previously reinforced high-probability action in extinction blocks two and four (both $p < .05$), whereas groups did not differ in the preceding reinforcement blocks (both $p > .35$). Although stressed participants chose the previously reinforced high-probability action also in the third extinction block significantly more often than controls ($p < .05$; Fig. 2), the block type \times group interaction did not reach significance for the third training block ($p = .62$) because control participants tended to chose the high-probability action also less often than stressed participants in the preceding reinforcement block (block 8; $p = .13$), which might have been a consequence of the previous extinction block that affected the

Table 1 Salivary cortisol and blood pressure responses to and subjective ratings of the stress vs. control condition.

	Control	Stress
<i>Salivary cortisol (in nmol/l)</i>		
Before treatment	8.1 \pm 1.0	7.7 \pm 0.8
1 min after treatment	8.6 \pm 1.0	8.4 \pm 0.9
25 min after treatment	6.8 \pm 0.7	13.8 \pm 1.9*
65 min after treatment	4.6 \pm 0.4	5.5 \pm 0.5
<i>Systolic blood pressure (in mmHg)</i>		
Before treatment	122.5 \pm 2.6	120.3 \pm 2.1
During treatment	120.3 \pm 2.4	136.2 \pm 2.6*
After treatment	117.5 \pm 2.4	119.0 \pm 1.9
<i>Diastolic blood pressure (in mmHg)</i>		
Before treatment	72.9 \pm 1.3	70.9 \pm 1.4
During treatment	72.7 \pm 1.4	84.0 \pm 1.7*
After treatment	72.2 \pm 1.4	69.9 \pm 1.4
<i>Subjective assessments</i>		
Stressfulness	3.8 \pm 1.4	47.2 \pm 5.3*
Painfulness	0.3 \pm 0.3	65.9 \pm 4.1*
Unpleasantness	7.8 \pm 2.2	60.9 \pm 5.1*

Subjective assessments were given on a scale from 0 ("not at all") to 100 ("very much"). Data represent means \pm SEM.

* Significantly higher than in the control group ($p < .01$).

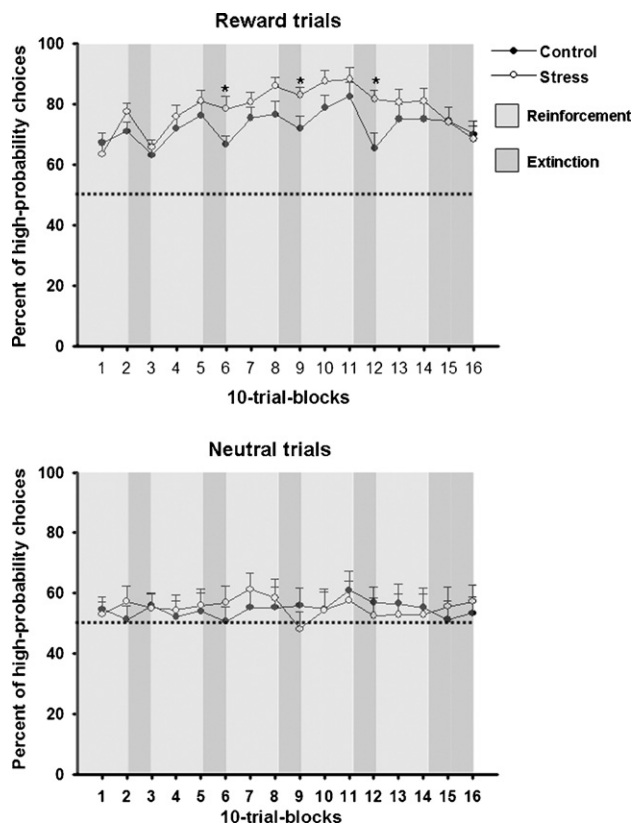


Figure 2 Percentage of high-probability actions in reinforcement and extinction blocks. (A) In reward trials, all participants increasingly favored the high-probability action associated with the reward over the referring low-probability action. Stressed participants chose the (non-rewarded) high-probability action in the second, third and fourth extinction block significantly more often than controls ($*p < 0.05$) suggesting that they were less sensitive to changes in the action-outcome contingencies. (B) In neutral trials, participants were indifferent between the high- and low-probability actions. The dotted line marks the percentage of high-probability actions of 50%, where subjects were completely indifferent between high- and low-probability actions. Data represent mean \pm SEM.

responding of controls but not the responding of stressed participants. In the first and in the last (i.e. fifth) training blocks there were no block type \times group interactions (both $p > .49$) indicating that the sensitivity to extinction was similar in stressed and control participants during initial learning and after repeated extinction blocks, respectively.

Same as in previous studies (Valentin et al., 2007; Schwabe and Wolf, 2009), reaction times were not modulated by stress or instrumental learning.

Finally, subjective pleasantness ratings confirmed that participants experienced the reward (average subjective pleasantness rating after learning ($M \pm SEM$): 64.5 ± 3.6) as significantly more pleasant than the neutral outcome (32.0 ± 3.8 ; $t(63) = 6.87$, $p < .001$; Table 2). Importantly, the stress manipulation had no influence on subjective food pleasantness and hunger ratings (all $p > .18$, Table 2).

Table 2 Hunger ratings and food pleasantness ratings before and after the learning task in the control and stress group.

	Control	Stress
<i>Hunger ratings</i>		
Before learning	67.81 ± 3.96	59.69 ± 4.83
After learning	64.07 ± 4.90	59.69 ± 5.67
<i>Pleasantness rating: reward</i>		
Before learning	74.06 ± 3.64	72.19 ± 4.28
After learning	66.25 ± 5.29	62.81 ± 4.98
<i>Pleasantness rating: common outcome</i>		
Before learning	33.75 ± 5.53	27.19 ± 4.19
After learning	14.69 ± 3.73	15.63 ± 3.89
<i>Pleasantness rating: neutral outcome</i>		
Before learning	61.56 ± 5.18	52.81 ± 3.89
After learning	38.75 ± 5.62	29.38 ± 4.38

Hunger and pleasantness ratings were given on a scale from 0 ("not at all") to 100 ("very much"). Data represent means \pm SEM. None of the group differences approached statistical significance.

4. Discussion

Our findings show that stress promotes behavioral persistence in humans. The exposure to a brief stressor before learning provoked the perseveration of rewarded responding under extinction, but did not influence the acquisition of the discrimination between rewarded and non-rewarded actions. The overall learning curves were not affected by stress suggesting that participants' instrumental learning capabilities per se remained unchanged.

An influence of stress on goal-directed vs. habit learning has been suggested in earlier studies (Dias-Ferreira et al., 2009; Schwabe and Wolf, 2009; Schwabe et al., 2010b). However, the design of these studies did not allow to disentangle stress effects on the formation of habits from those on the retrieval or expression of instrumental behavior as stress hormones were elevated both before learning and before the critical extinction test that revealed the goal-directed vs. habitual control of action. Moreover, there is evidence that stress may induce habitual responding without affecting learning processes (Schwabe and Wolf, 2010). In the present study, we assessed the character of instrumental behavior 'online' during learning which allowed us to examine stress-induced changes in instrumental action across the learning session and to demonstrate that stress enhances behavioral persistence after initial learning. At this point, however, it is to be emphasized that our extinction procedure degraded action-outcome, stimulus-outcome, and stimulus-response (i.e. habit) contingencies. Thus, it remains unclear which of these three associations was influenced by stress and we cannot conclude for sure that the observed effect of stress is an effect on habit formation. Our previous studies (Schwabe and Wolf, 2009, 2010; Schwabe et al., 2010b) indicated that stress and stress hormones facilitate habit behavior. The present findings show that stress increases resistance to extinction; the cause of the behavioral persistence may be its habitual form.

How can the observed behavioral persistence following stress be explained? According to Easterbrook's (1959) cue utilization hypothesis, emotional arousal narrows the range of cues that are attended to, reduces the availability of important information, allows single cues to guide behavior and may hence favor rather rigid behavior. At the neural level, stress and stress hormones impair neuroplasticity processes in the hippocampus and prefrontal cortex (Joels, 2006; Diamond et al., 2007), the brain areas that are implicated in goal-directed action, contingency learning and cognitive control (Balleine and Dickinson, 1998a; Corbit and Balleine, 2000; Koehlin et al., 2003; Valentin et al., 2007). Thus, it could be hypothesized that stress facilitates habit formation mainly by impairing competing goal-directed processes. However, this conclusion remains rather speculative in the absence of neuroimaging or lesion studies on the impact of stress on behavioral persistence or habit formation. Moreover, recent rodent findings indicate that (chronic) stress may cause structural changes both in the neural circuits underlying goal-directed action and in those supporting habit action, though in opposite directions (Dias-Ferreira et al., 2009).

There is also some evidence from rodent studies that stress may impair (fear) memory extinction (Akirav and Maroun, 2007; Izquierdo et al., 2006). However, these studies used relatively long stress-extinction intervals and assessed selectively how stress affects extinction learning. We are not aware of any rodent studies that alternated reinforcement and extinction sessions, as we did here, to examine the course of the stress-induced resistance to extinction. Given the opportunity to address endocrine, neural, and molecular mechanisms in rodents, such translational studies seem highly desirable.

The repeated assessment of the sensitivity of behavior to extinction allowed us to estimate when stress altered instrumental responding. Our data indicate that stress did not induce a general extinction deficit; rather the extinction deficit after stress was dependent on the amount of previous training. At the beginning, i.e. before frequent repetition enabled the formation of habits, the behavior of all (i.e., stressed and control) participants was sensitive to extinction. Stress made responding preservative under extinction after about 30 reinforced learning trials. Interestingly, the performance of control participants remained even after about 60 reinforced learning trials sensitive to the extinction procedure which might be due to the repeated presentation of extinction blocks after which a kind of new learning was required.

Although habits and behavioral persistence have often negative connotations, the persistence induced by stress appears to be rather adaptive in the present paradigm. Stressed participants responded after an initial learning phase primarily to the action that yielded the desired outcome in numerous trials before whereas the alternative action was never followed by the desired outcome. In other words, stress promoted behavior that led to favorable results in the past. This underlines that persistent or habitual behavior is not necessarily disadvantageous but may represent an efficient, cognitively less demanding type of action. This efficacy, however, comes at the price of a reduced sensitivity to situational changes which may prompt for changes in behavior.

While we relate the present findings to habitual instrumental learning, alternative conceptualizations are possible. For example, the reduced sensitivity to the extinction procedure after stress may be seen as stress-induced impairments in cognitive control (Steinhauser et al., 2007), cognitive flexibility (Alexander et al., 2007) and exploratory behavior (Berridge and Dunn, 1989). Alternatively, the present findings could be related to stress-induced rigidity (Cowen, 1952) or as an increase in perseverance which is known to be modulated by neurotransmitters such as dopamine that are released during stressful experiences (Cools, 2006). In addition to these cognitive effects, the exposure to the stressor may have resulted in numerous emotional or motivational changes that might have affected participants' performance. For example, it cannot be ruled out that stress led to a kind of fatigue, although the reaction time data provided no direct evidence for such an interpretation.

To summarize, the present study has shown that a brief stressor may reduce the sensitivity of instrumental responding to extinction. These findings extend earlier findings suggesting that stress favors rather rigid, less flexible behavior (Schwabe et al., 2010a) and could have important implications for addictive disorders which have been related to aberrant instrumental responding (Everitt and Robbins, 2005) and may be promoted by stress (Koob and Kreek, 2007).

Role of funding source

Funding for this study was provided by DFG grant SCHW1357/2-1; the DFG had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Conflict of interest

Both authors report no conflict of interest.

Acknowledgements

This work was supported by DFG grant SCHW 1357/2-1. We thank Carsten Siebert and Florian Watzlawik for assistance during data collection. We gratefully acknowledge the technical assistance of Tobias Otto.

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