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Acute psychophysiological stress impairs human associative learning

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ABSTRACT

Addiction is increasingly discussed as a disorder of associative learning processes, with both operant and classical conditioning contributing to the development of maladaptive habits. Stress has long been known to promote drug taking and relapse and has further been shown to shift behavior from goal-directed actions towards more habitual ones. However, it remains to be investigated how acute stress may influence simple associative learning processes that occur before a habit can be established. In the present study, healthy young adults were exposed to either acute stress or a control condition half an hour before performing simple classical and operant conditioning tasks. Psychophysiological measures confirmed successful stress induction. Results of the operant conditioning task revealed reduced instrumental responding under delayed acute stress that resembled behavioral responses to lower levels of reward. The classical conditioning experiment revealed successful conditioning in both experimental groups; however, explicit knowledge of conditioning as indicated by stimulus ratings differentiated the stress and control groups. These findings suggest that operant and classical conditioning are differentially influenced by the delayed effects of acute stress with important implications for the understanding of how new habitual behaviors are initially established.

1. Introduction

The ontology of addiction is often described as a series of associative learning processes (Everitt & Robbins, 2005) involving both operant and classical conditioning. Operant conditioning is an active learning process that is initially driven by goal-directed behaviors involving actions leading to a rewarding outcome; however, over time the behavior becomes habitual and actions are performed irrespective of the outcome (Dickinson & Balleine, 1994; Skinner, 1938a,b). In contrast, classical conditioning relies on passive learning of stimulus-outcome relations (Pavlov, 1927). Addiction (e.g. drug use) is thought to be influenced by operant conditioning in the following way: Whereas initial drug use is driven by a voluntary goal-directed process reinforced by the rewarding properties of the drug, later stages of addiction are characterized by habitual and compulsive drug use that continues despite adverse consequences (Everitt & Robbins, 2016). Pavlovian conditioning has been shown to interact with these operant conditioning processes through simple stimulus-outcome interactions, as drug-related cues predicting reward can enhance craving and compulsive tendencies observed in addicts. Thus, identifying the role of factors that facilitate initial operant and Pavlovian learning processes, which occur before habitual behaviors are established, is crucial for understanding individual variability in vulnerability to addiction.

Stress has long been known to be a major factor in the inception and development of addictive behavior, elevating drug self-administration and promoting relapse (Piazza & Le Moal, 1998; Sinha, 2008). Several human and non-human studies have demonstrated that habit formation, a key component in the emergence of addictive behaviors, is promoted by both chronic and acute stress (Dias-Ferreira et al., 2009; Everitt & Robbins, 2016; Graham, Yoon, & Kim, 2010; Koob, 2008; Schwabe & Wolf, 2009). Building on these studies, research in humans has focused on effects of stress on favoring habitual over goal-related behavior. In a series of studies in human subjects, Schwabe and Wolf (2009, 2010) exposed participants to acute psychophysiological stress or a control condition either before or after operant training tasks. Participants in the stress group showed more persistent habitual performance even in the absence of reward both when stress was induced before and after contingencies were learned (Schwabe & Wolf, 2009, 2010). A recent study (Pool, Brosch, Delplanque, & Sander, 2015) further employed a Pavlovian-Instrumental Transfer (PIT) task to show that stress increases the craving for a rewarding outcome without affecting the pleasure of consuming it – an important characteristic of addiction (Everitt & Robbins, 2016). The 3-stage PIT task employed (Talmi, Seymour, Dayan, & Dolan, 2008) taps three distinct processes implicated in habit formation. In the operant conditioning phase, the association between an action and reward is established via operant

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conditioning (Balleine, 2011; Skinner, 1938a,b). In the second, Pavlovian learning phase, a passive association is made between a stimulus and reward. Finally, during the subsequent extinction phase, habitual or transfer behavior is measured by strength and persistence of instrumental action in response to the Pavlovian stimulus in the absence of reward. In the study by Pool et al. (2015), participants were exposed to an acute stress or a no-stress control condition after the learning phase. Here the stress group mobilized more effort in response to the now-unrewarded Pavlovian stimulus than the control group, which was interpreted as increased cue-triggered 'wanting' (Pool et al., 2015). As this study focused on effects of stress on transfer, outstanding questions remain about effects of stress on learning processes that precede the establishment of habit, when simple associations between an action or a stimulus and a rewarding outcome are first acquired. Thus, the goal of the present study was to examine the effects of acute stress on the initial operant conditioning and Pavlovian conditioning stages of this 3-stage PIT task.

Based on previous research, there are a number of ways in which acute stress could influence initial reward learning. First, there is research suggesting that stress may have opposing effects on different phases of learning and transfer, reducing initial associative learning while enhancing reliance on habit once a habit has been formed. For example, a body of non-human animal literature suggests that stress reduces appetitive learning (Pielock, Braun, & Hauber, 2013; Shors, 2004). Yet results in humans have been more equivocal. Schwabe and Wolf (2009) found no effect of stress on initial learning of probabilistic contingencies for different rewarding stimuli; however, additional evidence provided some preliminary indication that stress might have a detrimental effect (Schwabe & Wolf, 2009). If stress has opposing effects on learning, given previous findings that stress enhances habit formation (Pool et al., 2015; Schwabe, Tegenthoff, Hoffken, & Wolf, 2010; Schwabe & Wolf, 2011), we would expect it to impair initial associative learning processes.

One reason for inconsistent findings with regard to effects of stress on learning may be that its effects on learning and memory do not depend only on the learning phase. They are also markedly influenced by the timing of the stressor relative to learning [for review see (Joels, Pu, Wiegert, Oitzl, & Krugers, 2006)]. An acute stressor activates two stress systems: (1) Immediate activation of a fast-acting stress system leads to a release of mostly catecholamines such as norepinephrine and dopamine. Activation of this system facilitates cognitive processes at the time of stress induction [for review see (Schwabe, Wolf, & Oitzl, 2010)]. (2) With a delay of up to one hour after stress induction, glucocorticoids (cortisol in humans) activate a gene-mediated pathway leading to an elevated processing threshold for incoming information (Herman, McKlveen, Solomon, Carvalho-Netto, & Myers, 2012). In other words, cognitive processes such as learning and memory are suppressed during this period (de Quervain, Roozendaal, & McGaugh, 1998; Kirschbaum, Wolf, May, Wippich, & Hellhammer, 1996). For consistency with the Pool et al. (2015) study, we aimed to examine effects of delayed stress on associative learning. As activation of the glucocorticoid pathway suppresses learning, we would again expect operant and Pavlovian learning processes to be suppressed by delayed stress.

Third, stress may not only differentially affect distinct stages of habit learning, but may also have different effects on learning rate and reward sensitivity as two independent components of reward-based learning (Huys, Pizzagalli, Bogdan, & Dayan, 2013). Previous research focusing on effects of stress on depression-related anhedonia suggests a detrimental effect of stress on reward responsiveness linked to learning - at least in some participants. When used as a stressor, threat of shock has been found to reduce preference for a high probability over a low-probability reward (Bogdan & Pizzagalli, 2006). Other studies have observed such a pattern of reduced reward responsiveness under stress *only* in participants high in stress reactivity (Berghorst, Bogdan, Frank, & Pizzagalli, 2013) or behavioral inhibition (Cavanagh, Frank, & Allen, 2011). Yet, notably, the opposite pattern of improved reward responsiveness has been observed in those low in behavioral inhibition (Cavanagh et al., 2011). Thus, we also aimed to examine effects of stress on both learning rate and reward sensitivity.

Taken together, previous studies suggest that the effects of acute stress on reward learning depend on the learning phase (acquisition vs transfer), the relative timing to the stressor (immediate vs delayed) as well as the reward learning component (learning rate vs reward sensitivity). Thus, the goal of the present study was to investigate the effect of *delayed* stress on initial stages of active operant and passive Pavlovian learning using a task that allows us to assess reward sensitivity. In particular we wished to determine the effects of stress on formation of associations that are distinct from, but contribute to, habitual behavior as operationalized in human PIT tasks (Pool et al., 2015; Talmi et al., 2008). For this reason, we examined effects of acute stress on behavior in the operant and classical conditioning tasks that comprised the first two stages of the 3-stage human PIT task described above (Talmi et al., 2008). These tasks are distinct from those employed in many studies of operant conditioning in that the associations learned are simple and learning occurs very rapidly (Pool et al., 2015; Talmi et al., 2008). For example, the association of an action and reward is learned after the first few encounters — very much as when a drug is taken for the very first time and the associated pleasurable experience is remembered immediately. Another advantage is that it allows us to investigate the willingness to exert physical effort rather than simply testing cognitive abilities. This is central to our goal of examining reward sensitivity because it allows us to measure how much work participants are willing to put into the task given a certain reward and whether this is affected by stress.

In the present study, two separate experiments investigated effects of acute stress on operant and Pavlovian learning as in (Pool et al., 2015). In Experiment 1a and 1b healthy undergraduate students performed a simple operant conditioning task in which they learned to squeeze a hand-grip to obtain a low (Experiment 1a) or high (Experiment 1b) monetary reward (Talmi et al., 2008). In Experiment 2 participants performed a simple Pavlovian learning task in which colored fractal patterns were associated with monetary reward. Both procedures were performed either following acute psychophysiological stress or in a stress-free control condition. For stress induction, participants were exposed to the commonly employed socially evaluated cold pressor test (SECPT) (Pool et al., 2015; Schwabe, Haddad, & Schachinger, 2008). We hypothesized that the delayed effects of acute stress during the first encounter of an action-outcome contingency would (a) decrease the effort and frequency with which the behavior is performed to obtain that reward (that is reward sensitivity is reduced), and (b) influence the extent of appetitive Pavlovian learning.

2. Experiment 1

2.1. Materials and methods

2.1.1. Participants

Prior to data collection, a power analysis was performed in order to determine the number of subjects. Assuming an effect size of $\eta^2 = 0.15$ based on previous research (Pool et al., 2015) and a repeated measures ANOVA, approximately 190 participants were necessary. A sample size of at last 200 allows for attrition, hence data collection was continued until the end of the academic term in which the minimum was reached.

214 participants (155 females, mean age: 21.59 ± 3.63 years) took part in Experiments 1a and 1b (102 and 112 participants respectively). All participants were compensated for their participation by course credit. Participants were asked not to eat, consume alcohol or caffeine and exercise two hours before the experiment. Testing was completed between 9 AM and 6 PM (Table 1). Participants were randomly assigned to stress and control conditions (103 and 111 participants respectively). The study was approved by the Human Research Ethics Board of the University of British Columbia.