Prolonged effects of acute stress on decision-making

(急性ストレスによる意思決定への遅延効果)

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Declaration

The research in this thesis is the author's own original work. I hereby declare that this thesis has not been submitted, either in the same or different form, to this or any other University for a degree.

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Abstract

Organisms have to adapt to a various change of environments in order to survive. In this adaptation process, physiological activity plays a significant role: Cardiovascular, endocrine, and immune systems mutually affect responses in other systems. Beyond actual threatening situations, organisms also need to protect themselves from potential threats. Thus, a threatening situation might continuously influence behaviors and cognition through the central nervous system—even during normalization of physiological states from hyperactivation induced by an earlier situation. Acute stress might play an important role in behavior and cognition later when acute physiological stress responses have disappeared. This study focuses on prolonged effects of physiological responses, evoked by exposure to acute stress, on reward-related decision-making.

Study 1 confirmed whether the serotonin (5-hydroxytryptamine) transporter (5HTT) gene-linked polymorphic region (5HTTLPR) genotype, one major genetic factor determining inter-individual differences in stress reactivity, affected cortisol-secretion reactivity to an acute stressor and whether reactivity returned to baseline within 90 min. Participants carrying double copies of S alleles, indicating high physiological reactivity under acute stress, and participants carrying S and L alleles, indicating low physiological reactivity, completed a stress task. Endocrine parameters and heart rate (HR) were measured before, during, and after the task. The result confirmed greater transient increases in glucocorticoid and HR response after the stress task in participants with SS alleles than in participants with SL alleles. Additionally, transient increases of such physiological responses returned to the baseline within 90 min., regardless of 5HTTLPR genotypes.

Study 2 investigated prolonged effects of physiological responses induced by acute stress on risk taking in decision-making. The stress task was administered as an acute stressor; thereafter, a decision-making task was performed in which participants needed to choose a sure option or a gamble option in gain and loss frame trials 2 hours after (non) exposure to the stressor. Increased cortisol, adrenaline, HR, and subjective stress levels validated the manipulation of acute

stress. Stressed participants made fewer risky choices only in the gain domain, but no effect of stress was shown in the loss domain. Deceleration of HR, reflecting attention, was greater for gains compared with losses only in the Stress group. Risk avoidance was determined by increased levels of cortisol caused by acute stress. These results suggested that physiological responses induced by acute stress might involve the prolonged effects of acute stress on decision-making.

Study 3 additionally investigated whether participants' inner states, affected by prior acute stress responses, specifically enhanced or reduced motivation for monetary reward in the decision-making task under risk (in Study 2). For this purpose, the study used a Pavlovian-instrumental transfer (PIT)-like experimental paradigm, in which a stress-related cue was presented decision-making task in Study 2. Then in Study 3, its influences on a stochastic learning task were examined. Results showed that prior acute stress enhanced effects of stress on amplifying the rate of choice of an advantageous option, selectively, in the Congruent group, associated between the stress-related cue and the advantageous choice. This result suggested that the enhancement of preference for a cautious option (Study 2) was caused by promoting motivation to obtain a reward. Furthermore, results of multiple-group structural equation modeling (SEM) suggested, even though statistical requirements were not adequately satisfied, that the association between cortisol reactivity and the magnitude of the PIT-like effects might later be mediated mainly by responses in the glucocorticoid system.

Present results revealed that acute stress promotes a cautious preference only for the gain domain in decision making under risk 2 h after stress onset. Based on the previous findings and the results of the present experiments, this cautious preference might be caused by inhibited impulsivity to a large monetary reward. Previous findings showed that the rapid effect of acute stress reduces the ability to evaluate situations, and that the organism can be affected by emotional stimuli immediately after the onset of acute stress and thus it can show emotional decisions due to lack of careful considerations. In contrast, the prolonged effect of acute stress prompts cautious preferences which might recover risky decision immediately after acute stress. Findings in the present thesis assumed that the potential role of

prolonged effects under acute stress helped an organism return a lost calm to its normal state.

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Chapter 1 Acute stress and decision-making under risk

1.1. Preface

To survive, organisms must adapt to various changes in their environments. Especially when they encounter threatening situations, these organisms must select appropriate behaviors and recover their calm. In this adaptation process, physiological activity plays a significant role: Cardiovascular, endocrine, and immune systems mutually affect responses in other systems and lead to appropriate behaviors to protect the organism from danger, in coordination with the activity of the central nervous system. I define a situation requiring these transient adaptations as acute stress and responses in this situation as acute stress responses.

Beyond actual threatening situations, organisms also need to protect themselves from potential threats. A threatening situation might continuously influence behaviors and cognition—even during normalization of physiological states from hyperactivation induced by a threatening situation. It is not clear whether acute stress might mediate behavior and cognition later when acute physiological stress responses have disappeared.

This study focuses on prolonged effects of physiological responses, evoked by exposure to acute stress, on reward-related decision-making. The thesis begins with a review of findings on physiological responses evoked by acute stress and decision-making in the face of risk. Next, potential pathways between activities of physiological systems and the brain under acute stress are overviewed. Then, arguments about prolonged effects of acute stress on decision-making—a primary purpose of this thesis—are summarized. Based on these overall findings, I reported three studies for my purpose. In Study 1, preliminary research confirms whether prolonged response affects physiological reactivity to an acute stressor and whether reactivity later returns to baseline. Study 2 examines prolonged effects of acute stress on decision-making under risk. Study 3 examines three issues in reward-

related decision processes: goal-directed processing versus habitual processing; decision by description versus decision by experience; and motivational enhancement to obtain a reward. I concluded this thesis by providing a possible model for effects of acute stress on decision-making under risk based on these emprical findings.

1.2. Physiological responses induced by acute stress and decision-making

After exposure to an acute stressor, two physiological responses occur—in the sympathetic-adrenal-medullary (SAM) system (Cannon, 1929) and in the hypothalamic-pituitary-adrenal cortex (HPA) system (Selye, 1936), both playing important roles in energy production when an organism faces a threat. The SAM system elicits transient reaction of the sympathetic nervous system, resulting in the release of catecholamine, such as adrenaline and noradrenaline, through the adrenal medulla and autonomic nerve endings, respectively. These responses are called "fight-or-flight responses," and the responses support aggressive and combative or fleeing behavior. On the other hand, the HPA system leads to the slow secretion of cortisol, a glucocorticoid of the steroid hormones secreted from the adrenal cortex. Cortisol secretion is activated by secretion of adrenocorticotropic hormone (ACTH) by the pituitary gland through the release of corticotrophin-releasing hormone from the hypothalamus. To adapt effectively to the environment and use resources to win the struggle for survival, the HPA system consolidates physiological and psychological influences. These two systems play a central role in regulating many homeostatic systems, including cardiovascular and immune systems. Additionally, substances involved in these systems, such as catecholamine and glucocorticoid, have facilitating and inhibiting influences on the central nervous system, related to cognitive and emotional processes underlying decision-making (Preston et al., 2007; Starcke & Brand, 2012; Wolf, 2012).

Beginning with Ben Zur & Breznitz in 1981, most studies have reported the exposure to acute stress enhanced risk taking (Lighthall, Mather, & Gorlick, 2009; Pabst, Brand, & Wolf, 2013a; Preston, Buchanan, Stansfield, & Bechara, 2007;

Starcke, Wolf, Markowitsch, & Brand, 2008, 2012; van den Bos, Harteveld, & Stoop, 2009). Previous studies have specifically focused on effects of acute stress on risk in decision-making by using a conventional experimental paradigm of lottery tasks, in which participants choose a riskier option with larger reward and lower probability or a safer option with smaller reward and higher probability of obtaining monetary gains or preventing monetary losses. Recent findings have suggested that effects of acute stress on risk preference depend on whether potential outcomes are gains or losses. Some studies observed increased risk-taking only for the loss domain but decreased risk-taking for the gain domain under acute stress, resulting in a strengthened "reflection effect" (Kocher, Pahlke, & Trautmann, 2013; Porcelli & Delgado, 2009). The reflection effect means that risk preferences in decision-making are reversed, depending on domains; generally, greater preference for risky options is linked to losses rather than gains (Kahneman & Tversky, 1979).

Although many studies have reported effects of acute stress, previous findings are mixed and complicated. One study found risk preferences only for gains, and stress had no effect on loss (Buckert, Schwieren, Kudielka, & Fiebach, 2014). In contrast, others reported effects of acute stress on less risk-taking only for the loss domain, with no effect on the gain domain (Clark, Wright, Rome, Fairchild, Dunn, & Aitken, 2012; Pabst, Brand, & Wolf, 2013b). Although some studies found null effects of acute stress on risk decision-making (Gathmann et al., 2014; Lempert, Porcelli, Delgado, & Tricomi, 2012), effects on risk-taking of exposure to acute stress, depending on the domain, remain plausible. Whether acute stress affects the gain or loss domain in decision-making under risk remains unclear.

1.3. The prolonged effects of acute stress on decision-making

One possible factor explaining these inconsistent results is time-dependent effects elicited by exposure to acute stress. Previous literature has shown that, even hours after stress induction, acute stress can robustly affect many facets of higher-order cognitive functions (Diamond et al., 2007; Henckens et al., 2012; 2011;

Vinkers et al., 2013; Yamakawa, 2016). This section overviews previous studies on prolonged effects of acute stress via glucocorticoid responses.

Prolonged effects of acute stress are that biological responses induced by acute stress affect cognition and emotion even later, when transit physiological responses have returned to baseline. In human studies, Henckens et al. (2011) indicated prolonged effects of acute stress on the modulation of prefrontal working memory processing. The prolonged effects of glucocorticoid improved working memory performance in a numerical n-back task and increased working memory-related activation of the dorsolateral PFC. These results were consistent with a rodent study in which the administration of corticosterone—mainly glucocorticoids in rats—in the PFC enhanced glutamatergic transmission in the PFC, and stress improved a working memory task 4 hours later (Yuen, Liu, Karatsoreos, Feng, McEwen, & Yan, 2009).

Furthermore, researchers have examined prolonged glucocorticoid effects of acute stress not only on working memory but also on processing of emotional stimuli and regulation of emotion. Henckens et al. (2010) revealed that prolonged effects of stress influence emotional processing via a sensitized amygdala for a few hours after acute stress. Prolonged glucocorticoid effects suppressed the reactivity of the amygdala only to positive stimuli, whereas rapid effects suppressed the reactivity to both positive and negative emotional stimuli. Furthermore, researchers suggested that this slow response enhanced connectivity between the amygdala and medial PFC, which are known to play significant roles in the regulation of negative emotion (Ochsner & Gross, 2001). The slow response also suppressed amygdala activity during the regulation of emotional responses to negative stimuli (Beauregard, Lévesque, & Bourgouin, 2001; Kompus, Hugdahl, Ohman, Marklund, & Nyberg, 2009). Thus, these prolonged effects of acute stress can cause a robust, powerful influence on cognitive and emotional functions.

It is assumed that cognitive and emotional functions play important roles in decision-making under risk. Cognition aids careful consideration of decisions in an adaptive direction through the complex assessment of short- and long-term costs and benefits of actions. Emotions are supposed to guide adaptive decisions via

somatic markers evoked by experiencing and anticipating reward and punishment. Vinkers et al. (2013) reported the only human study on the slow effects of stress on decision-making. They observed that prolonged effects of acute stress increased acceptance of unfair offers for maximizing reward in the Ultimatum game. In contrast, rapid effects of acute stress reduced the acceptance of the offers. They concluded that prolonged effects of stress led to upregulation of the cognitive self-control system in decision-making in social situations. However, no study has examined the prolonged effects of acute stress on decision-making under risk. Therefore, this study mainly aimed to examine whether prolonged effects of acute stress influence decision-making under risk. The study also aimed to clarify characteristics of prolonged effects on decision-making compared with rapid effects of acute stress.

1.4. The purpose of the present thesis

As explained, inconsistent findings for effects of acute stress on decision-making possibly result from the temporal aspect of physiological responses elicited by acute stress. Indeed, prolonged effects induced by cortisol response strongly influence emotional and cognitive processes related to decision-making under risk, and prolonged effects on decision-making under risk remain unclear. The present thesis purposed to reveal whether physiological response elicited by exposure to acute stress prolonged and continuously influenced decision-making under risk. To achieve these purposes, I investigated whether or not exposure to acute stress affect risk-taking in decision-making under risk. Furthermore, if physiological stress responses affect risk-taking, the degree of influence might alter depending on physiological stress reactivity. Thus, the present thesis must consider the following points.

1.4.1. Psychological processes involved

For detailed consideration of the prolonged effects of acute stress on decision-

making under risk, I focus on psychological processes. Risky decision-making performance could be interpreted by various aspects of psychological processes. One aspect is whether prolonged effects of acute stress are based on goal-directed action or habitual action (Schwabe & Wolf, 2011). In other words, acute stress can facilitate flexible action in seeking goals or inflexible action in avoiding alterations. A second aspect is whether effects of acute stress on risk-taking occur through experiential or descriptive processes (Hertwig & Erev, 2009). Elucidating which process influences risk-taking might lead to understanding whether later risk-taking is caused by learning the relationship between feedback and options or the evaluation of the relative values of options. Finally, the thesis considered whether the risk-taking tendency emerged through motivational enhancement for reward to demonstrate that acute stress influences the activity of reward system some hours after onset.

Accordingly, the current thesis examines these issues based on the assumption that prolonged effects of acute stress mediate risk-taking in decision-making, as indicated by previous findings.

1.4.1.1. Goal-directed processing vs. habitual processing

The learning process is the basis of decision-making under risk related to obtaining a reward. Contemporary learning theories explain performance of reward-related actions is controlled by two learning processes. One is the acquisition of a goal-directed process, and the other is the acquisition of habits. These two processes are characterized by sensitivity to changes in the motivational value of the outcome and changes in contingency gradation of an action and outcomes. A goal-directed process encodes the relationship between an action and outcomes. This process is assumed to be sensitive to the contingency between action and outcome and have high flexibility to environmental changes. In contrast, a habitual process builds an association between responses and preceding stimuli without any link to outcomes that responses engendered. This process is assumed to be insensitive to the contingency between action and outcome and have low flexibility to environmental changes (Balleine & Dickinson, 1998; Dickinson, 1985;

Schwabe & Wolf, 2011). Most previous findings consistently revealed that acute stress prompts habitual behaviors immediately after exposure to stress (Schwabe, Tegenthoff, Höffken, & Wolf, 2010; Schwabe & Wolf, 2011). Additionally, according to a previous review by Diamond et al. (2007), prolonged stress reduces neuroplasticity in the neural circuits supporting goal-directed behavior, especially in the PFC, through excessive activation of dopamine receptors (Nemeroff, Bremner, Foa, Mayberg, North, & Stein, 2006; Olff, Langeland, & Gersons, 2005). However, these findings are based on the study of post-traumatic stress disorder, which is a maladaptive symptom after exposure to extreme stress. Diamond et al. (2007) mentioned that the inhibition in PFC by acute stress might recover fully to baseline, depending on the intensity of the stressor. It is possible that prolonged effects of acute stress influence goal-directed and habitual processes, but this is not clear.

1.4.1.2. Decision by experience vs. description

The second issue is whether effects of acute stress on risk taking occur through experiential or descriptive processes (Hertwig & Erev, 2009). Decision-making under risk is discriminated between decisions prompted by description versus decisions prompted by experience. Both kinds of decisions can be understood as opposite entries on a continuum of modes of decision-making in uncertainty. Decisions by descriptive processes relate to evaluations of the magnitude of reward and probability and involve a priori probabilities. Contrarily, decisions by experiential processes relate to learning information from actual experiences of outcomes of choices and involve statistical probabilities. Descriptive processes affect top-down decisions based on alteration of cognition to values of options; alternatively, experiential processes promote bottom-up decisions based on trial-by-trial cognitive and affective experiences. Buckert et al. (2014) discussed the importance of distinguishing between descriptive decisions and experiential decisions when investigating stress effects on economic decision-making. Previous studies on rapid effects of acute stress reported that acute stress prompted the enhancement of decisions by description compared with decisions by experience (Buckert et al., 2014). Furthermore, a recent study observed that rapid effects of

acute stress decreased decisions by description for losses but increased decisions for gains; in contrast, acute stress did not influence decisions by experience regardless of gains or losses (Wegier & Spaniol, 2015). These results indicate that rapid effects of acute stress specifically influence the descriptive process. Even so, enhanced and inhibited effects differ depending on the domains of gain or loss. However, whether prolonged effects of acute stress can bias risk-taking via the descriptive process is unclear.

1.4.1.3. Enhancement of motivation to obtain rewards vs. reduction of attraction of rewards

Third is the motivation to obtain a reward in decision-making under risk. Decision-making under risk is demonstrated by achieving pleasant or avoiding unpleasant states, such as the learning process leading to reward or punishment. Therefore, motivation to obtain a reward has a significant role in modulated decision-making. In theories of behavioral economics, motivation to obtain a reward is a major determining factor of a value of a decision, as is the other factor—a weight for low probability. Excessive motivation to obtain a reward prompts preference of a risky choice compared with a sure choice because excessive motivation focuses on the amount of reward and because a value of risky choice is enhanced, compared with a sure choice.

Most previous findings consistently suggested that acute stress immediately increased motivation to obtain a reward, resulting in the enhancement of reinforcement learning (Cavanagh, Frank, & Allen, 2011; Lighthall et al., 2012; Lighthall et al., 2009; Mather, Gorlick, & Lighthall, 2009; Petzold, Plessow, Goschke, & Kirschbaum, 2010; Preston et al., 2007; Starckeet al., 2008; van den Bos et al., 2009). Additionally, some studies observed that acute stress might cause increased dopaminergic signaling in the striatum (Mather & Lighthall, 2012; Starcke & Brand, 2012), resulting in increasing reward salience and risky decisions. However, it is not clear whether any bias in decision-making under risk caused by prolonged effects of acute stress emerges through enhancement of motivation to obtain monetary gain or through reduced attraction to monetary gain.

This thesis examines this issue using a computational model from a conventional reinforcement learning algorithm, the Q-learning model based on the Rescorla-Wagner model (1972). Theories of reinforcement learning have provided a strong framework for understanding how agents update their value functions based on the mismatch between expected and actual rewards, namely rewards prediction error, assuming actions are chosen to maximize expected rewards. If motivation to obtain a reward is enhanced, agents prompt the updating of their value functions (Sutton & Barto, 1998; Daw, & Doya, 2006; Corrado & Doya, 2007).

1.4.2. Individual differences of stress reactivity

For detailed consideration of prolonged effects evoked by physiological stress response, I must reveal the time-dependent reactivity of cortisol, especially the point when transit response of cortisol, elicited by acute stress, returns to baseline. Many studies have reported that cortisol response returned to baseline approximately 60 min after exposure to acute stress (Buckert et al., 2014; Pace et al., 2009). In these physiological stress responses, however, individuals differ widely, and genetic factors determine some portions of individual differences.

One major genetic factor determining inter-individual differences in stress reactivity is the serotonin (5-hydroxytriptamine, 5HT) transporter (5HTT) gene polymorphism, which mediates reuptake and recycling of released serotonin following acute stress. In humans, the 5HTT gene has a polymorphism termed *serotonin transporter gene-linked polymorphic region* (*5HTTLPR*) (Heils et al., 1995). In lymphoblast cell lines, the promoter sequence has a long (L) or short (S) form of 5HTTLPR, and promoter activity of 5HTT is due to these allelic variants (Heils et al., 1996; Heinz & Goldman, 2000).

Indeed, genetic factors strongly modulate reactivity of the endocrine system, such as the HPA system. The serotonin system is located to moderate cortisol reactivity evoked by stress via neural activity at the suprahypothalamic level and at the level of the HPA system. Gotlib, Joormann, Minor, and Hallmayer (2008) demonstrated that physiological stress response of cortisol was more enhanced in individuals with the SS genotype than in those with the LL genotype. However,

their results did not reveal the point when the response in an individual with the SS genotype, which is a cortisol responder, returns to baseline.

1.5. Empirical studies for the present thesis

Prolonged effects of acute stress have different features than rapid effects because time-dependent responses of the glucocorticoid system, induced by acute stress, temporally influence decision-making, both immediately and later. For investigation of prolonged effects induced by acute stress on decision-making, it is necessary to confirm that rapid reactivity has returned to baseline. As described above, physiological stress reactivity differs according to the individual. I focus on the 5HTT genotype, which is a major genomic factor determining inter-individual differences in stress reactivity. The purpose of Study 1 was to examine whether the 5HTT genotype affected reactivity of cortisol to an acute stressor and confirm that reactivity returned to baseline regardless of the 5HTT genotype. I measured cortisol concentrations as an index of activity of the HPA system, and heart rate (HR) and heart rate variability (HRV) served as indices of activity of the SAM system. I used the Trier social stress test (TSST) (Kirschbaum, Pirke, & Hellhamme, 1993), a well-defined, standardized acute psychological stress task. This task is known to evoke stress responses reliably with activation of the HPA system activity and SAM system activity (Allen, Kennedy, Cryan, Dinan, & Clarke, 2014).

Based on results of Study 1, Study 2 investigated whether exposure to acute stress influenced later decision-making after stress response returned to baseline. Some studies investigated prolonged effects on modulation of working memory processing and emotion regulation using administration of hydrocortisone for activation of glucocorticoid (Henckens et al., 2011; Henckens et al., 2010). Vinkers et al. (2013) recently reported that the only study on humans concluded that prolonged effects of stress led to upregulation of the cognitive self-control system in decision-making in social situations. However, no study has examined prolonged effects of acute stress on decision-making under risk. Cognitive and emotional

functions play important roles in decision-making under risk for careful consideration of decisions in adaptation and guidance for adaptive decisions. Study 2 examined the hypothesis that exposure to acute stress later affects risk-taking in decision-making, and an increase of cortisol induced by acute stress relates to regulated risk-taking. For this hypothesis, I used a decision-making task including risk. In the decision-making task, participants chose one option from two alternatives—a sure or a gamble option. I compared rates of gamble choice in Stress and Control groups.

In addition, the following two psychological processes are investigated for beneficial suggestions for understanding prolonged effects of acute stress on decision-making. The first is whether alterations in risk taking caused by acute stress are based on habitual or goal-directed action (Schwabe & Wolf, 2011). To examine this issue, I manipulated the expected value (EV) of a safer option and a riskier option in each decision-making trial. If acute stress makes habitual action dominant, participants should show within-individual consistent tendencies of risk preference or risk avoidance, regardless of differences in EV. If acute stress facilitates goal-directed action, participants should become more sensitive to EVs of options, and they should make risk-seeking or risk-avoiding choices depending on relative comparisons of the EVs of the options.

The second issue is whether effects of acute stress on risk taking occur through experiential or descriptive processes (Buckert et al., 2014). To examine this issue, I measured transient deceleration of HR as an orienting response, a typical physiological response to feedback signals in decision-making (Bradley, 2009; Osumi & Ohira, 2009). If the experiential account is correct, HR deceleration should correlate with risk-taking after exposure to acute stress.

In Study 3, the following points related to psychological processes were investigated. The first issue is whether prolonged effects on risk-taking in Study 2 emerged from enhanced motivation to monetary gain or attraction to a larger monetary gain. For elucidating this point, I investigated attitudes to a neutral stimulus related to stress response, namely, enhancing motivation or attraction. Some research has reported attitude to stimulus as related to stress response using

a PIT paradigm. PIT is a phenomenon in which a previously neutral stimulus (a conditional stimulus: CS) that has been linked with adaptively significant events, either positive or negative (an unconditional stimulus: US), may exert control over instrumental actions (Kruse, Overmier, Konz, & Rokke, 1983; Trapold & Overmier, 1972). Past research has observed PIT not only using a monetary reward, but also an aversive stimulus as an US. Campese, McCue, Lázaro-Muñoz, LeDoux and Cain (2013) have shown that participants reduced their motivation to a neutral stimulus linked to an aversive US. In this study, through manipulation of linking neutral stimulus and prolonged stress response, I investigated whether prolonged effects enhanced motivation to the neutral stimulus related to stress response, or reduced motivation.

I modified the experimental paradigm of PIT as follows. Participants in Study 2 continued to take part in Study 3. Study 3 was planned and conducted a week or more after Study 2. I manipulated stress-related cues (background colors of the display where options for choice were presented) during the decision-making task in Study 2. I established two groups at the stage of the stochastic learning task in Study 3, a Congruent group and an Incongruent group. In the stochastic learning task, participants chose one option from two alternatives to obtain monetary gains and avoid monetary losses. The expected value for reward was higher for the advantageous option than for the other, disadvantageous one. The stress-related cue in the Congruent group was associated with the advantageous option; in contrast, the stress-related cue in the Incongruent group was associated with the disadvantageous option. In Study 2, if participants had enhanced motivation to gain reward caused by acute stress in the decision-making task, the stress-related cue might be associated with motivation to obtain a reward. Alternatively, if participants had reduced motivation for reward from the previous decision-making task, the effects of the stress-related cue would cause fewer choices of the advantageous option in the Congruent group.

In addition, two psychological processes, namely, goal-directed versus habitual and descriptive process versus experience process, are investigated. First, I examined whether prolonged effects enhanced goal-directed or habitual action. As

above, goal-directed, but not habitual process is assumed sensitive to the contingency between action and outcome and high flexibility to environmental change (Balleine & Dickinson, 1998; Dickinson, 1985; Schwabe & Wolf, 2011). I manipulated the contingency degree between options and reward/punishment in the stochastic learning task. Participants in the Stress and Control groups performed both the Contingent condition and the Random condition. In the Contingent condition, an advantageous option led to monetary gain at a probability of 70% and led to monetary loss at a probability of 30%. Another disadvantageous option was associated with gain and loss at an invented probability (30% gain and 70% loss). In contrast, in the Random condition, gain and loss rates were delivered randomly for both options (50% gain and 50% loss). This manipulation was introduced to examine whether predicted effects of the stress-related cue were mediated by goal-directed processing or by habitual processing. Goal-directed processing is significantly elicited by a situation with high contingency. If effects of the stress-related cue occurred via goal-directed processing, participants would be significantly influenced by cues when their choices could alter probabilities of obtaining or losing the reward. Namely, the stress-related cue would bias choices of options only in the Contingent condition. In contrast, if effects from the stress-related cue on the stochastic learning task were via habitual processing, participants would automatically be influenced by the stress-related cue, regardless of contingency for the reward. The stress-related cue would bias option choices in the same manner for both Contingent and Random conditions.

Moreover, the present study measured the transient deceleration of HR, as an orienting response, to reveal whether predicted effects from the stress-related cue on the choice of options occurred through experiential or descriptive processes, as in Study 2. The stress-related cue might amplify responses to gain-and-loss feedback; therefore, it could bias future choices through learning processes (the experience account). In contrast, the stress-related cue might affect evaluations of contingency between options and outcomes (gain/loss), and thus, this could bias choice behavior without learning processes (the description account). Phasic HR deceleration can be interpreted to indicate increased attention to a stimulus

enhancing defensive or appetitive motivation (Sánchez-Navarro et al., 2006; Bradley, Codispoti, Cuthbert, & Lang, 2001). If the experiential account is correct, HR deceleration should correlate with the rate of choice of the advantageous option. If the description account is correct, HR deceleration is a response accompanying top-down processing.

This thesis reported three experiments investigating prolonged effects of acute stress on decision-making. In Study 1, I focused on the 5HTT genotype, which is a major genomic factor determining inter-individual differences in stress reactivity. For the purpose, I examined whether the 5HTT genotype affected reactivity of cortisol to an acute stressor and confirmed that reactivity returned to baseline regardless of the 5HTT genotype adjusting stress response. In Study 2, as a main experiment in this thesis, I investigated prolonged effects of acute stress on decision-making, including risk. I measured the gamble choice rate in a lottery decision-making task performed two hours after exposure to acute stress and compared it between the Stress and Control groups. Furthermore, the two psychological processes, namely, goal-directed process versus habitual process and descriptive process versus experiential process, were investigated for beneficial suggestions for understanding prolonged effects of acute stress on decision-making. In Study 3, I examined whether the prolonged effects on risk-taking in Study 2 emerged by enhancing motivation to monetary gain or attraction to a larger monetary gain. I measured the choice rate to stimulus-related stress response using the stochastic learning task, including contingency, and compared the Stress group with the Control group. Similar to Study 2, the two psychological processes were demonstrated. As a result of these experiments, I proposed prolonged effects of acute stress on motivational process in decision-making and the possible time-dependent model describing physiological and neural mechanisms underlying effects of acute stress on decision-making.

Chapter 2 Psychophysiological stress reactivity modulated by 5HTTLPR (Study 1)

2.1 Introduction

This purpose of the preliminary study was to determine whether the serotonin (5-hydroxytryptamine) transporter (5HTT) gene-linked polymorphic region (5HTTLPR) genotype affects temporal reactivity of cortisol secretion in an acute stress situation. As overviewed in Chapter 1, many studies suggest an association between the 5HTTLPR genotype and physiological reactivity to acute stressors, particularly in the HPA system. Some human studies reported the association between the 5HTTLPR genotype and the reactivity of an acute psychological stress task (Gotlib et al., 2008; Ohira et al., 2009). Furthermore, the study revealed that, compared with SL and LL genotypes, individuals with the SS genotype had enhanced cortisol secretion in response to acute psychological stressors (Miller, Wankerl, Stalder, Kirschbaum, & Alexander, 2013).

Despite many such reports, results of examining the association between 5HTTLPR and cortisol reactivity to acute stress are inconsistent. For example, Gotlib et al. (2008) observed a 45-min continued increase in the only individual with the S allele immediately after exposure to acute stress in an experimental protocol. Moreover, Way and Taylor (2010) observed a significantly increased level of cortisol with the SS genotype 10–30 min after a public interview and returned response. Possibly, task differences, task durations, and measurement times among studies have led to inconsistent results. Furthermore, as explained in Chapter 1, the transit increase of glucocorticoid, including cortisol evoked by acute stress, prolonged effects on the central nervous system after 90 min. However, modulation of the 5HTTLPR genotype on reactivity of cortisol during the recovery period remains unclear. Thus, to elucidate how the 5HTTLPR genotype influences reactivity of cortisol, I must employ a standardized acute stress task and then assess temporal variation of cortisol during the recovery period.

Data in Study 1 was published in *Scientific Reports* (Yamakawa et al., 2015).

My main purpose was to examine whether the 5HTT genotype affected reactivity of cortisol to an acute stressor and whether reactivity returned to baseline within 90 min. I measured cortisol concentrations in peripheral blood. Additionally, heart rate (HR) and heart rate variability (HRV) served as indices of SAM system activity. For this purpose, I used the Trier social stress test (TSST) (Kirschbaum et al., 1993), a well-defined, standardized acute psychological stress task (Allen et al., 2014).

2.2 Method

2.2.1 Participants

Nine participants with the S allele and nine with the SL allele participated in the present study. All participants were male, right-handed, native Japanese, and undergraduate or graduate students of Nagoya University (age (mean ± standard error); SS: 20.78 ± 0.26 years, SL: 21.00 ± 0.25 years). None of the participants was suffering from any chronic illnesses and none were taking medications known to influence immunity. Only men were studied to avoid influences of the menstrual cycle on any physiological stress responses in women (Kudielka & Kirschbaum, 2005). All participants provided their informed consent to participate in the study, in accordance with university policy. The study was approved by the Ethics Committee of Nagoya University.

For determining genotypes, genomic DNA was extracted with a DNA Extractor WB-Rapid Kit (Wako Inc., Osaka, Japan) from frozen blood samples collected from the participants. I analyzed samples using polymerase chain reaction according to previously reported methods, generating L (528 bp) and S (484 bp) fragments 4. Individuals carrying double copies of the S allele (SS genotype) and individuals carrying the S and L alleles (SL genotype) were identified. Polymerase chain reactions (PCR) were performed using the primers 5' GGCGTTGCCGCTCTGAATGC and 5'-GAGGGACTGAGCTGGACAACCAC in a 25 ml solution containing 100 ng genomic DNA, 0.4 mM dNTPs, 0.2 mM of each primer, 1.25U of Takara LA Taq polymerase (Takara Bio Inc., Otsu-shi, Japan), and GC

Buffer I (Takara Bio Inc., Otsu-shi, Japan). Initial denaturation at 95°C for 5 minutes was followed by 35 cycles of denaturation at 95°C for 30 seconds, annealing at 61°C for 30 seconds, and extension at 72°C for 1 minute. The PCR products were then analyzed on a 2% agarose gel stained with ethidium bromide. The amplification products for the L allele and the S allele were 528 bp and 484 bp, respectively (Lesch et al., 1996). I compared stress responses in the SS (n = 9) and SL (n = 9) genotypes, as the proportion of LL genotypes is small in the Asian population (Mizuno et al., 2006).

To evaluate participants' levels of trait anxiety as a potential confounder, I asked the participants to complete a Japanese version (Nakazato & Mizuguchi, 1982) of the State-Trait Anxiety Inventory (STAI) Speilberger, Gorusch, & Lushene, 1970).

2.2.2 Biological measures

Blood samples were collected in ethylenediamine tetraacetic acid (EDTA) tubes to determine changes in the proportion of NK cells among peripheral circulating lymphocytes before and after the TSST. Two-color flow cytometry was performed. The whole-blood lysis method was used to stain the NK cells with a fluorescein isothiocyanate (FITC)-conjugated anti-CD16 antibody (Ab) (DakoCytomation, Carpinteria, CA) as well as a R-phycoerythrin (RPE)-conjugated anti-CD56 Ab (DakoCytomation). Lymphocytes were identified by gating on low forward scatter (related to cell surface area) and 90° side scatter (related to cell granularity). Percentages of these cells in total lymphocytes per sample were obtained based on the lymphocyte gate from the FSC/SSC plots by FACSCanto II flow cytometer (Becton Dickinson, Franklin Lakes, NJ) using FACSDiva software (Becton Dickinson).

Additional blood samples were collected in EDTA tubes and centrifuged at 3,000 × g for 10 min to determine changes in cortisol levels in the plasma before and after the TSST; the plasma was then separated and stored at -80°C until analysis occurred. Cortisol plasma concentration was measured using a cortisol ELISA kit (Oxford Biochemical Research Inc., Oxford, MI). Here, the intra-assay

coefficient of variation was 3.4–3.7%, and the inter-assay coefficient of variation was 3.8–6.4%. Limit of detection was 0.3μg/ml.

Cardiodynamic activity was recorded using an electrocardiogram (ECG) at 500 Hz using an MP 100 system (Biopac Systems Inc., CA, USA) with Ag/AgCL electrodes placed on the extremities. Analysis of ECG waveforms was performed using AcqKnowledge software for MP 100. After rejection of artifacts in the ECG waveforms, HR and inter-beat-interval data were acquired during the baseline period, at three periods during the stress task (0–10, 10–15, and 15–20 min) and at each rest period. The inter-beat-interval data were subsequently analyzed to yield HRV. Data from each participant were subjected to ocular inspection and only completely artifact-free data were used for estimation of the inter-beat-intervals. The inter-beat-interval data were resampled at 4 Hz to obtain equidistant time series values. A power spectrum density was then obtained through a fast Fourier transformation of the tachogram. In connection with the fast Fourier transformation, the data were detrended linearly and filtered through a rectangular window. Power spectrum integral was studied in two major frequency bands, the HF (0.15–0.5 Hz) and LF (0.05–0.15 Hz) components. The former is related to respiratory sinus arrhythmia and is exclusively attributable to parasympathetic influence reflecting vagal activity, and in the latter case, the LF component mirrors the baroreceptor feedback loop that controls blood pressure and appears to reflect both sympathetic and parasympathetic activity. Consequently, the HF component and relative contributions of LF and HF power (LF/HF), which reflect sympathovagal balance, were considered (Xhyheri, Manfrini, Mazzolini, Pizzi, & Bugiardini, 2012).

2.2.3 Stress task (the TSST)

The TSST includes a fake speech as well as a mental arithmetic task (Kirschbaum et al., 1993). This is a standardized procedure for the induction (in laboratory settings) of acute psychological stress associated with the HPA system and autonomic nervous system arousal (Dickerson & Kemeny, 2004). After the

participants were introduced to the TSST (1 min), they were given 10 min to prepare themselves for a speech about school life (5 min), followed by a mental arithmetic task in front of an audience (5 min). The participants were told that they would be videotaped for further analysis of their behavior.

2.2.4 Procedures

The participants were instructed to eat a light breakfast on the morning of the experiment; caffeinated beverages were not allowed. They were also instructed to paste a monoanesthetic seal at the location of the cannula insertion in their arms by qualified medical staff about 1h before the experimental sessions to reduce pain. Participants suffering from an infectious illness within 2 weeks of the experiment were rescheduled.

For minimum confounds in the form of diurnal variations in hormone levels, experimental sessions for both conditions started at the exactly same time between 9:00 a.m. and 15:00 p.m. for each participant. Furthermore, experimental time (morning or afternoon) was counterbalanced between participants. The session was composed of a baseline period, the TSST, and 4 rest periods (Figure 2.1). After the participants entered the experiment room, a cannula was inserted into the forearm vein of the non-dominant arm. Next, electrodes for electrocardiographic measurements were attached. After a first rest period of 10 min, the first blood sample was taken as baseline sample, and the participants were asked to fill out a questionnaire. In this questionnaire, the participants were asked to subjectively evaluate stress intensity on visual-analog scales (0–100%) as a psychological measure of subjective stress level. TSST instructions were then provided (speech followed by a simulated interview). Following this, the participants prepared their speech (10 min) and were then exposed to a simulated interview (5 min) conducted by two interviewers in front of a video camera, followed by a mental arithmetic task (5 min). Immediately after the task, a second blood sample was taken and the participants again filled out the questionnaire. Finally, the participants read newspapers during the 90 min rest period. After each blood sample was taken and

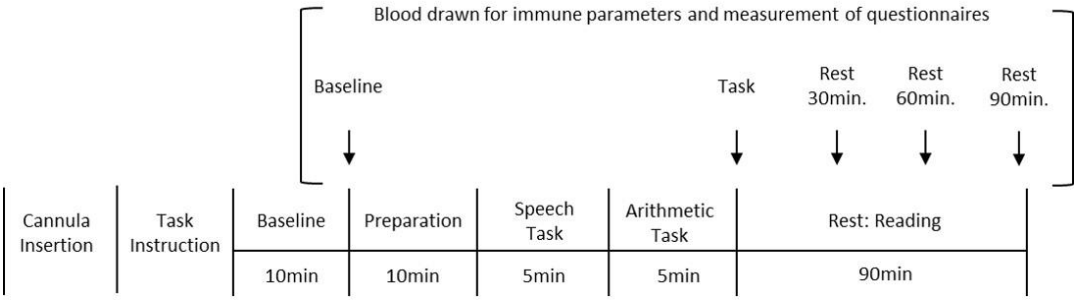

Figure 2.1. Experimental protocol of the present study.

the participants again filled out the questionnaire. Finally, the participants read newspapers during the 90 min rest period. After each rest period (30, 60, and 90 min after the completion of the TSST), the third, fourth, and fifth blood samples were taken and the questionnaire was filled out for a final time. ECG was measured continuously throughout the experimental session. After the end of the procedure, the electrodes and cannula were removed by qualified medical staff and the participants fully debriefed and thanked.

2.2.5 Statistical analysis

The present data were analyzed using repeated-measures analyses of variance (rmANOVA) with a between-participants factor of Group (SS genotype vs. SL genotype) and a within-participants factor of Period (at Baseline, Task, and Rest30min, Rest60min, Rest90min), with regard to intensity of stress, cortisol, lymphocyte and cytokine data. Cardiovascular data was also analyzed using rmANOVA with a between-participants factor of Group and a within-participants factor of Period (at Baseline, Task10min, Task 15min, Task 20min, Rest 30min, Rest 60min, Rest 90min). The sphericity assumption of errors was tested by

Mauchly's sphericity test. If the assumption was not sufficient, the Greenhouse–Geisser epsilon correction factor, ε (Jennings & Wood, 1976), was used to modify the degree of freedom for the F-test. In cases where significant interactions were found, post hoc analyzes using Bonferroni tests ($p < .05$) were conducted to examine which combinations of data points differed significantly. Effect sizes are presented as parietal η^2-values ($\eta_p{}^2$).

2.3 Results

2.3.1 Psychological measure

Intensity of stress collected during the stress task and rest periods are presented in Table 2.1. An rmANOVA revealed a significant main effect of Period ($F(1.99, 37.83) = 17.70$, $p < 0.05$, $\eta_p^2 = 0.48$). Post hoc analyzes ($p < 0.05$) indicated that perceptions of stress after the task were higher than at baseline. However, the interaction between Group and Period was not significant ($F(1.99, 37.83) = 0.26$, *n.s.*, $\eta_p^2 = 0.14$).

2.3.2 Physiological measures

For cortisol concentrations, there was a significant interaction between Group and Period, $F(4, 60) = 2.55$, $p < .05$, $\eta_p^2 = 0.15$, as shown in Figure 2.2. Cortisol levels significantly increased after the task compared to at baseline or during the rest periods, but only in the SS group. No such effect occurred for the SL group ($p < 0.05$). In additionally, no difference was the cortisol in rest period compared than in the baseline.

Cardiovascular data collected during the stress task and rest periods are presented in Figure 2.3. A significant interaction between Group and Period for change in HR was found ($F(2.23, 35.75) = 3.29$, $p < 0.05$, $\eta_p^2 = 0.17$). Post hoc analyzes ($p < 0.05$) found that HR changes in the SS group were greater during

execution of the speech tasks as compared to the SL group. Additionally, HR changes were greater in the SS group during the tasks than at baseline or during rest periods, but no such difference was observed in the SL group. Table 2.2 depicts HF components and the LF/HF ratio of HRV at baseline, task periods ($Task_{10min}$, $Task_{15min}$, and $Task_{20min}$) and rest periods ($Rest_{30min}$, $Rest_{60min}$, and $Rest_{90min}$). There were no significant main effects or interactions for the HF components or LF/HF ratio ($F(6, 96) = 1.04$, n.s., $\eta_p^2 = 0.61$; $F(3.44, 55.05) = 1.32$, *n.s.*, $\eta_p^2 = 0.76$).

Table 2.1. Intensity of stress.

	Group	Baseline	Task	Rest 30min.	Rest 60min.	Rest 90min.	Effect
Intensity of Stress (%)	SS	29.33 (5.94)	57.22 (7.70)	22.67 (6.42)	22.44 (6.12)	20.22 (6.56)	n.s.
	SL	28.89 (5.58)	57.44 (6.23)	28.67 (5.67)	31.33 (7.92)	24.00 (6.81)	

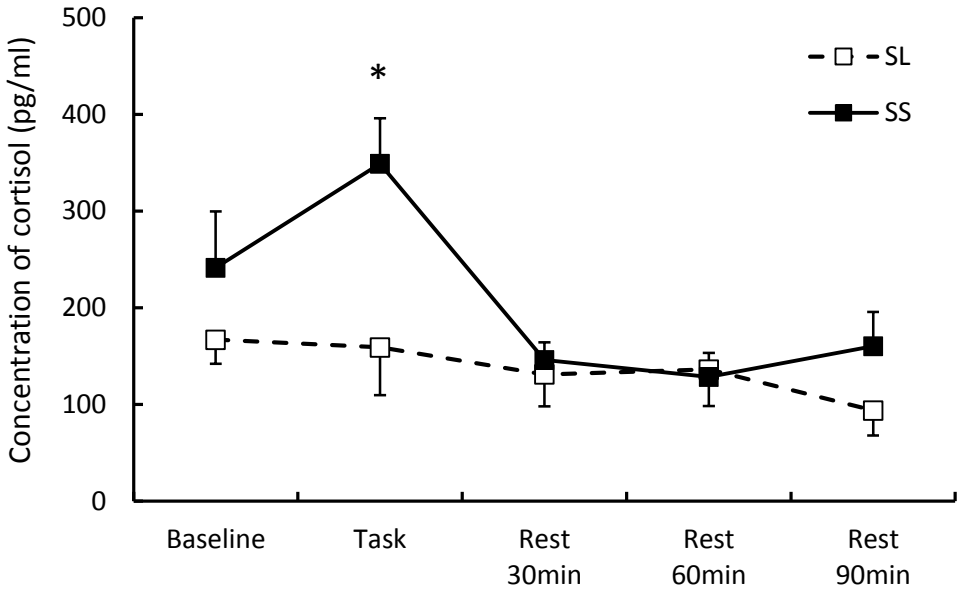

Figure 2.2. Cortisol concentrations for each group.

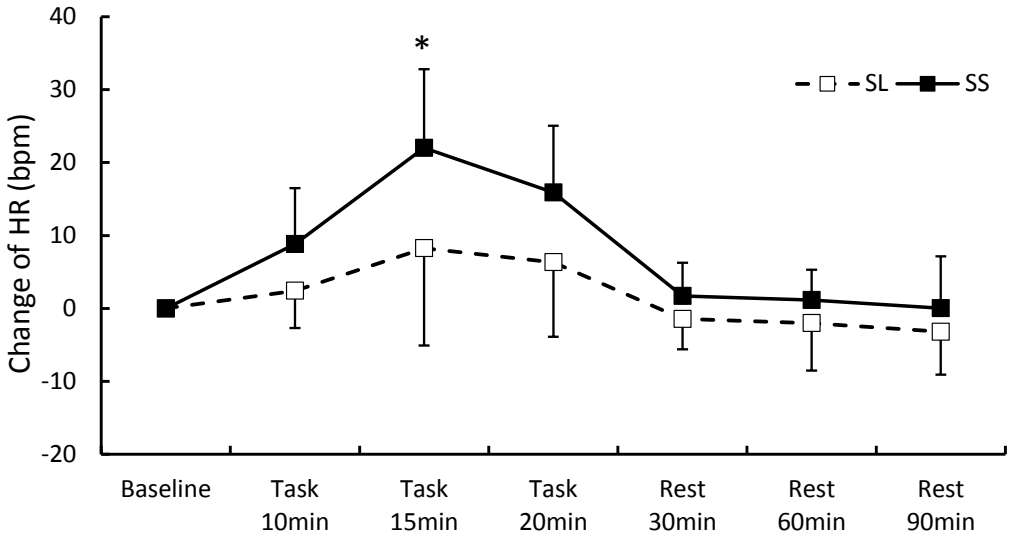

Figure 2.3. Changes of HR through experimental sessions.

Table 2.2. The high frequency (HF) component and low frequency (LF)/HF ratio

	Group	Baseline	Task 10min.	Task 15min.	Task 20min.	Rest 30min.	Rest 60min.	Rest 90min.	Effect
HF components (%)	SS	0.57 (0.12)	0.43 (0.16)	0.34 (0.14)	0.33 (0.15)	0.42 (0.19)	0.38 (0.18)	0.38 (0.11)	*n.s.*
	SL	0.38 (0.22)	0.37 (0.22)	0.28 (0.13)	0.29 (0.16)	0.38 (0.16)	0.34 (0.17)	0.31 (0.19)	
LF/ HF ratio	SS	1.05 (0.47)	1.79 (0.69)	3.28 (1.68)	3.20 (2.24)	2.13 (0.87)	2.86 (1.77)	2.03 (0.80)	*n.s.*
	SL	3.02 (2.77)	3.21 (2.34)	3.54 (1.92)	3.75 (2.83)	2.24 (0.96)	2.64 (1.01)	4.37 (4.02)	

2.4 Discussion

My main purpose was to examine whether the 5HTT genotype affected reactivity of cortisol to an acute stressor and whether reactivity returned to baseline within 90 min. I measured cortisol concentrations in peripheral blood. Additionally, HR and heart rate variability served as indices of SAM system activity. For this purpose, I used TSST, a well-defined, standardized acute psychological stress task.

Consistent with Gotlib et al. (2008), the present study revealed that an immediate, increased cortisol concentration under acute stress was clearly pronounced in 5HTTLPR SS carriers as compared to L carriers. Researchers have demonstrated in animals that serotonin activates the HPA system by stimulating the corticotropin-releasing factor, triggering ACTH release, and stimulating corticosteroid secretion (Fuller et al., 1996). Indeed, serotonin has been found to enhance negative feedback control of cortisol (Porter, Gallagher, Watson, & Young, 2004). Moreover, mice with the serotonin transporter gene removed have been found to exhibit increased HPA system response to acute stress (Li et al., 2004). In contrast, no increase in cortisol was observed 90 min after acute stress. This result confirmed that the glucocorticoid response returns the baseline exposure to acute stress later, when the prolonged glucocorticoid effects occur after acute stress, regardless of 5HTTLPR genotypes.

I observed greater transient increases in HR after the stress task in SS allele participants than in SL allele participants. Although the effect was not statistically significant, the SS group showed increased stress reactivity of the LF/HF ratio, an index of relative sympathetic nervoous activity. Previous studies have shown that sympathetic nervous system activation mediating the mobilization of monocytes is greater in S allele carriers than in L allele carriers (McCaffery, Bleil, Pogue-Geile, Ferrell, & Manuck, 2003; Way & Taylor, 2011). Serotonin neurotransmitter function in S allele carriers might be reduced via increased firing rates of serotonin neurons (Barton et al., 2008) and the downregulation of inhibitory 5HT1A receptors (Hariri & Holmes, 2006). In addition, Ohira et al. (2009) reported that SS allele

participants showed stronger reactivity in blood pressure and epinephrine secretion and greater activation in stress-related brain regions such as the hypothalamus, which regulates HPA and SAM axes. However, as with the cortisol concentration, these indices return to baseline after acute stress.

Chapter 3 Prolonged effects of glucocorticoid on decision-making under risk (Study 2)

3.1 Introduction

Study 1 indicated that the difference reactivity of physiological response by the serotonin (5-hydroxytryptamine) transporter (5HTT) gene-linked polymorphic region (5HTTLPR) genotype returns to baseline 90 min after acute stress onset. This confirmed normalization of physiological response evoked by acute stress after 90 min. Study 2 examined the relationship between physiological response to acute stress and later decision-making.

Previous literature has shown that, even hours after the induction of stress, acute stress can robustly affect many facets of higher-order cognitive functions, including emotional memory (Diamond et al., 2007), selective attention to emotional stimuli (Henckens et al., 2012), working memory (Henckens et al., 2011), and altruistic punishment in an economic game (Vinkers et al., 2013). These findings led us to infer the possibility of acute stress also affecting decision-making under risk in longer time ranges. If this inference is correct, an important question regarding underlying biological mechanisms is whether the strength of physiological responses (HPA and SAM responses) (Diamond et al., 2007) to acute stress at an early stage can determine the strength of later stress effects on bias toward risk-taking in decision-making. The present study explored this issue with an experiment measuring typical physiological indices of stress and risky choices in a lottery decision-making task performed 2 hours after exposure to acute stress.

The second possible cause of inconsistency in effects of acute stress on risk-taking is extensive individual differences in physiological stress reactivity. This study focused on one major genetic source of individual differences in stress reactivity, that is, 5HTT. Individuals with the SS genotype showed greater activation of stress-related brain regions (Ohira et al., 2009) and secretions of both

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Data in Study 2 was published in *Frontiers in Human Neuroscience* (Yamakawa et al., 2016).

cortisol (Gotlib et al., 2008) and inflammatory cytokines (Yamakawa et al., 2015) in response to acute stressors than did individuals with SL and LL genotypes. If physiological stress responses affect risk taking, 5HTTLPR can affect the degree of influence; individuals with S alleles could show stronger linkages between acute stress and risk taking. People with S alleles recruited from the population showed higher neuroticism and lower tendencies toward financial risk taking (Kuhnen, Samanez-Larkin & Knutson, 2013). Therefore, I investigated whether 5HTTLPR differentiates the association between physiological stress responses and risk taking.

Furthermore, psychological mechanisms through which acute stress can affect later decision-making are of much interest. Here, I should consider two important theoretical decision-making issues. The first is whether effects of acute stress on risk taking occur through experiential or descriptive processes (Buckert et al., 2014). Descriptive processes affect decisions based on alteration of cognition to values of options; alternatively, experiential processes promote decisions based on trial-by-trial cognitive and affective experiences (Hertwig & Erev, 2009). To examine this issue, I measured transient deceleration of HR, as an orienting response, a typical physiological response to feedback signals in decision-making (Bradley, 2009; Osumi & Ohira, 2009). If the experiential account is correct, HR deceleration should correlate with risk taking after exposure to acute stress. If the descriptive account is correct, acute stress should independently affect HR deceleration and risk taking. The second issue is whether alterations in risk taking caused by acute stress are based on habitual action or goal-directed action (Schwabe & Wolf, 2011). Acute stress can facilitate strategic deliberation of individuals in preferring or avoiding risk to seek their inner goals. To examine this issue, I manipulated the expected value (EV) of a safer option and a riskier option in each decision-making trial. In some trials, the riskier option provided a higher EV than the safer option, whereas in other trials, the EV of the riskier option was lower than that of the safer option, or the EVs of both options were identical. If acute stress makes habitual action dominant, participants should show within-individual consistent tendencies of risk preference or risk avoidance regardless of

differences of EVs. However, if acute stress facilitates goal-directed action, participants should become more sensitive to the EVs of options, and they should make risk-seeking or risk-avoiding choices depending on relative comparisons of the EVs of options. An exploration of these theoretical issues can provide beneficial suggestions for understanding prolonged effects of acute stress on decision-making.

3.2 Method

3.2.1 Participants

In the present study, 28 Japanese male undergraduates at Nagoya University (age range 18–22 years; mean = 19.92; S.D. = 1.20) participated. They were randomly assigned to a Stress group and a Control group. Two participants in the Stress group were excluded from the analysis because of technical problems in the data collection. None of the participants suffered from any chronic illnesses and none took any medications. Participants were advised not to smoke or drink alcohol on the days they participated in the experiments. The Ethics Committee of Nagoya University approved the study. In accordance with guidance for human subjects, all participants signed an informed consent to participate in the study.

Individuals carrying double copies of S alleles (SS genotype), S and L alleles (SL genotype), and L alleles (LL genotype) were identified. Genomic DNA was extracted from fresh or frozen blood samples collected from participants using a DNA Extractor WB-Rapid Kit (Wako Inc., Osaka, Japan). Polymerase chain reactions (PCR) were performed using the primers 5'-GGCGTTGCCGCTCTGAATGC and 5'-GAGGGACTGAGCTGGACAACCAC in a 25 ml solution containing 100 ng genomic DNA, 0.4 mM dNTPs, 0.2 mM of each primer, 1.25U of Takara LA Taq polymerase (Takara Bio Inc., Otsu-shi, Japan), and GC Buffer I (Takara Bio Inc., Otsu-shi, Japan). Initial denaturation at 95°C for 5 minutes was followed by 35 cycles of denaturation at 95°C for 30 seconds, annealing at 61°C for 30 seconds, and extension at 72°C for 1 minute. The PCR products were then analyzed on a 2% agarose gel stained with ethidium bromide. The

amplification products for the L allele and the S allele were 528 bp and 484 bp, respectively (Lesch et al., 1996). In the present study, 14 participants had the SS genotype (with two participants excluded), 12 had the SL genotype, and no participants had the LL genotype. Because the proportion of the LL genotype is small in the Japanese population (Mizeno et al., 2006), I compared participants with the SS genotype (Stress group: N = 6, Control group: N = 8) to those with the SL (Stress group: N = 6, Control group: N = 6).

3.2.2 Decision-making task

At the beginning of each trial, participants were shown a message indicating a starting amount of money. They had to choose a sure or a gamble option for each trial. The sure option meant keeping the amount of money given at the beginning in the Gain frame trials and losing the amount given at the beginning in the Loss frame trials. The gamble option was shown as a pie chart depicting the probability of Hit (red) or Miss (blue) and the amount of monetary reward or loss (see Figure 3.1). Options were presented for 2 seconds, followed by a response stress-related cue to prompt participants to make a choice. After the choice, a feedback signal (Keep, Hit, or Miss) was indicated. For this manipulation, I set conditions at three different EV levels between gamble and sure options: a large EV gamble with a larger EV of the gamble option than of the sure option; a small EV gamble with a smaller EV of the gamble option than of the sure option; and an equal EV gamble with the same EV of the gamble option as of the sure option. Therefore, the independent variables in this task were Domain (Gain or Loss) and EV of gamble option (Large, Equal, and Small). In addition, I manipulated the probability of hit outcome when the gamble option was chosen (see Table 3.1). Gain and Loss trials were presented as separate blocks, with counterbalanced orders across participants in each group. Within a block, conditions of the EV gamble option were presented randomly.

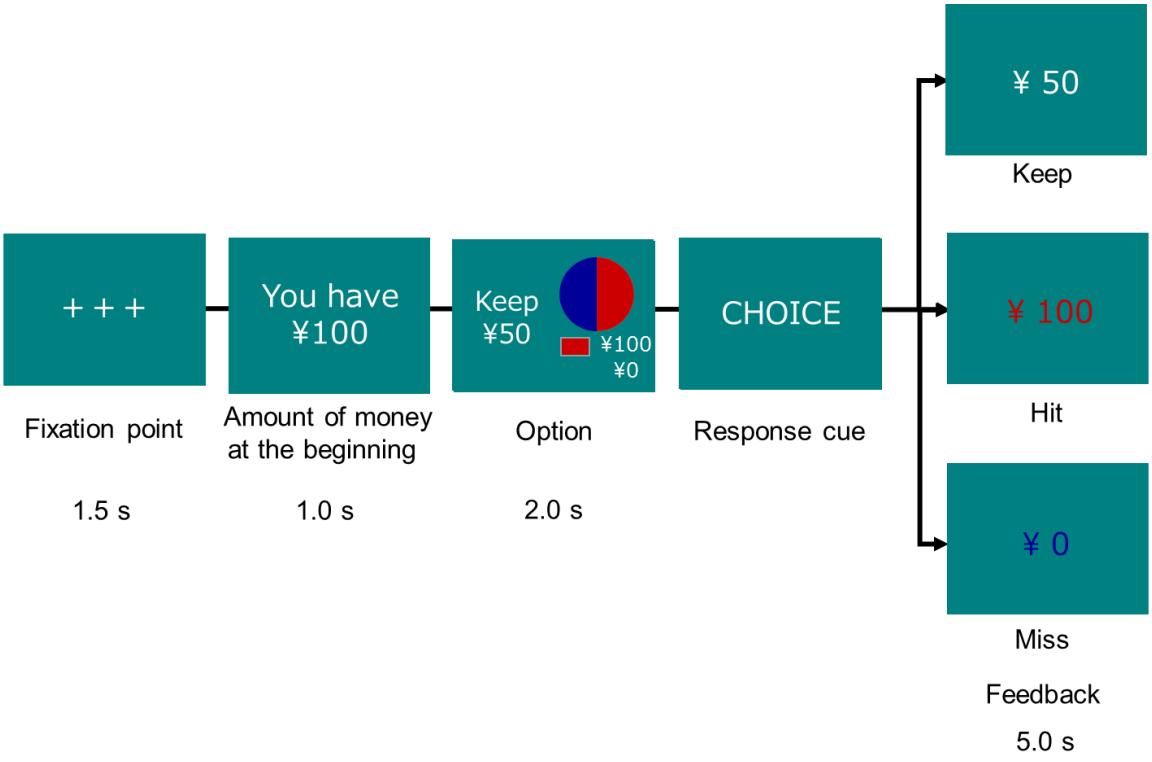

Figure 3.1. Decision-making task.

3.2.3 Procedures

Experimental sessions started at either 09:00 a.m. or 12:00 p.m. and lasted for four hours. To control the effects of diurnal variations in cortisol secretion, the numbers of participants allocated into early and late experimental sessions were counterbalanced between the Stress group and the Control group. Participants were instructed to eat a light breakfast on the morning of the experiment but not to drink caffeinated beverages. Participants suffering from an infectious illness within two weeks of the experiment were rescheduled.

The timeline of experimental session for both groups is presented in Figure 3.2. After participants entered the experimental chamber, a cannula was inserted into their non-dominant forearm vein by qualified medical staff. Next, electrodes for electrocardiographic measurements were attached to the same arm. After the first

Table 3.1. Attribute of gambling option.

(a) Gain domain.

40% (Keep = + 200 yen) Amount of money = 0			60% (Keep = + 360 yen) Amount of money = 0	
Hit	Miss	EV level	Hit	Miss
+ 700	0	Large	+ 800	0
+ 600	0		+ 700	0
+ 500	0	Equal	+ 600	0
+ 300	0	Small	+ 500	0
+ 200	0		+ 400	0

(b) Loss domain.

40% (Keep = - 300 yen) Amount of money = 500			60% (Keep = - 240 yen) Amount of money = 600	
Hit	Miss	EV level	Hit	Miss
+ 200	- 500	Large	+ 200	- 600
+ 100	- 500		+ 100	- 600
0	- 500	Equal	0	- 600
- 100	- 500	Small	- 100	- 600
- 200	- 500		- 200	- 600

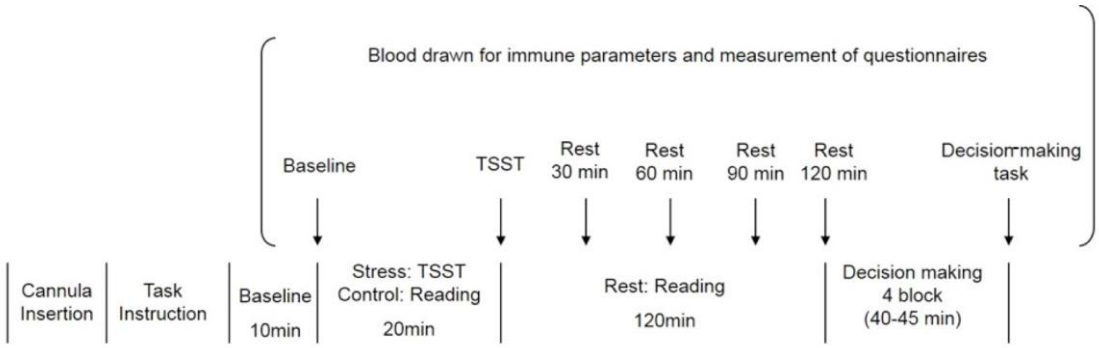

Figure 3.2. Experimental protocol of the present study.

rest period of 10 minutes, the first blood sample was taken as a baseline, and participants were asked to rate subjectively their intensity of stress. Thereafter, instructions for the "Trier Social Stress Test" (TSST) (Kirschbaum et al., 1993) were provided. The TSST includes a simulated speech task and a mental arithmetic task. This procedure is standardized for the induction of acute psychological stress in laboratory settings associated with activation of the HPA system and autonomic nervous system. After participants were introduced to the TSST (1 minute), they were given 10 minutes to prepare a speech on school life (5 minutes), followed by a mental arithmetic task performed in front of an audience (5 minutes). Participants were told they would be videotaped for further analysis of their behaviors. Following this, participants were given 10 minutes to prepare for their speech. They were then exposed to a simulated interview (5 minutes) conducted by two interviewers in front of a video camera, followed by a mental arithmetic task (5 minutes). Immediately after the task, a second blood sample was taken, and participants again subjectively rated their stress. Participants read newspapers during the 120-minute rest period. After each rest period (30, 60, 90, or 120 minutes after completing the TSST), the third, fourth, and fifth blood samples were taken; again, participants rated their stress subjectively. Finally, instructions for the decision-making task were given, and participants conducted the decision-making task after several practice trials. Cardiodynamic activity was measured

continuously throughout the experimental session. After the procedure ended, the electrodes and cannula were removed by qualified medical staff, and participants were fully debriefed and thanked. The experimental session in the Control group was identical to that in the Stress group, except that participants read newspapers for 20 minutes instead of focusing on the TSST.

3.2.4 Psychological and behavioral measures

Participants were asked to evaluate the intensity of their stress on a visual analog scale (0–100%) after the baseline period, the TSST task period, each rest period, and the decision-making period. In addition, I calculated the response bias in each block of the decision-making task.

3.2.5 Measurement of cortisol and adrenaline

Blood samples were collected in EDTA tubes and centrifuged at 3,000 × g for 10 minutes to measure cortisol levels in the plasma. The plasma was then separated and stored at −80°C until the analysis. The plasma cortisol concentration was measured using a cortisol ELISA kit (Oxford Biochemical Research Inc., Oxford, MI, USA). The intra-assay coefficient of variation was 3.4–3.7%, and the inter-assay coefficient of variation was 3.8–6.4%. The limit of detection was 0.3 μg/ml. To determine adrenaline levels, blood samples were collected in serum separator tubes and centrifuged for 15 minutes. The serum was removed and then kept at −80°C until analysis. The concentration of adrenaline in the serum was measured using an HPLC-electrochemical detector (ECD) (CoulArray; ESA Biosciences Inc., Chelmsford, MA, USA). The inter-assay coefficient of variation was less than 7.0%. The limit of detection was 0.1 ng/ml.

3.2.6 Cardiac measures

Cardiodynamic activity was recorded using an electrocardiogram (ECG) at 500 Hz, using the MP 100 system (Biopac Systems Inc., CA, USA) and Ag/AgCL

electrodes on the extremities. The analysis of ECG waveforms was performed using AcqKnowledge software for MP 100 (Biopac System Inc., CA, USA). After the rejection of artifacts in ECG waveforms, HR and inter-beat-interval data were derived during the baseline period (10 minutes), the stress tasks period (15–20 minutes), each rest period (30 minutes), and the decision-making period (40–45 minutes). To analyze cardiac data in the decision-making task, inter-beat intervals were obtained from deviations between R-waves and converted into beats per minute (bpm). HR in bpm was averaged in half-second intervals and deviated from the one-second baseline preceding the feedback onset. Initial deceleration was assessed as a minimum value in 0–3 seconds of the feedback presentation period in each trial. As is known, HR deceleration reflects attentional orienting governed by parasympathetic activity (Bradley, 2009; Osumi & Ohira, 2009). For this reason, I focused on examining the outcome-related reactivity of HR induced by feedback signals of hit and miss.

3.2.7 Experimental design and statistical analysis

To certify that the TSST evoked acute stress responses, data showing HR, cortisol, adrenaline, and subjective stress levels during the TSST were analyzed using 2 (Group: Stress vs. Control) x 2 (Genotype: SS vs. SL) x 7 (Period: Baseline, TSST, $Rest_{30\ min}$, $Rest_{60\ min}$, $Rest_{90\ min}$, $Rest_{120\ min}$ Rest periods, Decision-making task) repeated-measures analyses of variance (rmANOVA). Group and Genotype were between-participant factors and Period was a within-participant factor. To analyze decision-making, the rates of gamble choice were administrated for a 2 (Group: Stress vs. Control) x 2 (Genotype: SS vs. SL) x 3 (EV level of gamble option: Large, Equal, and Small) rmANOVA. Group and Genotype were between-participant factors, and EV level was a within-participant factor. Cardiac data for feedback in the decision-making task were analyzed using a 2 (Group: Stress vs. Control) x 2 (Genotype: SS vs. SL) x 2 (Domain: Gain vs. Loss) x 2 (Outcome: Hit vs. Miss) x 3 (EV level of gamble option: Large, Equal, and Small) rmANOVA. Group and Genotype were between-participant factors and Domain, Outcome and EV level were within-participant factors. The sphericity assumption of errors was tested by

Mauchly's sphericity test. If the assumption was not sufficient, the Greenhouse–Geisser epsilon correction factor, ε (Jennings & Wood, 1976), was used to modify the degree of freedom for the F-test. In cases where significant interactions were found, post hoc analyzes using Bonferroni tests ($p < .05$) were conducted to examine which combinations of data points differed significantly. Effect sizes are presented as η^2-values.

To examine the association between physiological acute stress responses and decision-making and to determine the influences of 5HTTLPR genotypes on the association, I performed exploratory analysis. Multiple-group structural equation modeling (SEM) was conducted using physiological parameters as predictors for rates of gamble choice in decision-making across 5HTTLPR genotype (for details, see 3. 3. 3.). Considering the sample size of the present study, the overall model fit was assessed using chi-square/degree of freedom (df) ratio, goodness-of-fit index (GFI), and root mean square error of approximation (RMSEA). A chi-square/df ratio ≤ 0.20, a GFI ≥ 0.95, and an RMSEA ≤ 0.05 are considered the standard of a good fit (Schermelleh-Engel, Moosbrugger, & Müller, 2003).

3.3 Results

3.3.1 Manipulation check of acute stress

The results of the psychological data are presented in Table 3.2. An rmANOVA revealed a significant interaction between Group and Period, ($F(3.21, 70.66) = 7.56$, $p < 0.05$, $\eta_p^2 = 0.26$). Post hoc analyses ($p < 0.05$) indicated that the perception of stress after the TSST task was higher than that at the baseline in the Stress group. A significant interaction between Group and Period was observed for cortisol, ($F(3.67, 80.68) = 10.62$, $p < 0.05$, $\eta_p^2 = 0.18$) (Figure 3.3). The cortisol level significantly increased after the TSST task compared with the level at baseline or levels during rest periods in the Stress group but not in the Control group ($p < 0.05$). A significant interaction between Group and Period for HR was found ($F(3.90, 85.76) = 16.30$, $p < 0.05$, $\eta_p^2 = 0.43$) (Figure 3.4). Further analyses ($p < 0.05$) indicated that the

increase of HR in the Stress group was greater during speech tasks compared with the control group. Adrenaline concentration as an index of activation of the sympathetic nervous system showed a significant interaction between Group and Period, ($F(6, 132) = 7.29$, $p < 0.05$, $\eta_p^2 = 0.25$) (Figure 3.5). Post hoc analyses ($p < 0.05$) indicated that the adrenaline level after the TSST task in the Stress group was higher than that in the Control group, but no difference was observed during rest periods. All these indices consistently clarified that the stress task used in this study elicited typical, robust psychological and physiological (SAM and HPA) acute stress responses. Three-way interactions of Group, Period, and Genotype for those indices did not reach significance ($F = 1.20–1.77$, *n.s.* $\eta_p^2 = 0.05–0.08$).

Table 3.2. Intensity of stress.

		Baseline	TSST	Rest 30 min	Rest 60 min	Rest 90 min	Rest 120 min	Decision-making
Control	SS	0.69 (1.20)	1 (0.73)	1.55 (0.74)	1.26 (0.81)	1.00 (0.62)	1.16 (0.73)	1.24 (0.52)
	SL	1.48 (0.80)	1.283 (1.13)	1.73 (0.86)	1.98 (0.27)	1.83 (0.34)	1.77 (0.67)	1.83 (0.29)
Stress	SS	2.33 (2.40)	5.55 (2.28)	3.18 (0.95)	1.87 (1.33)	3.22 (1.95)	3.17 (2.49)	2.86 (1.30)
	SL	1.77 (1.31)	5.383 (2.46)	1.95 (1.07)	1.7 (1.25)	1.33 (0.81)	1.57 (1.24)	1.64 (1.03)

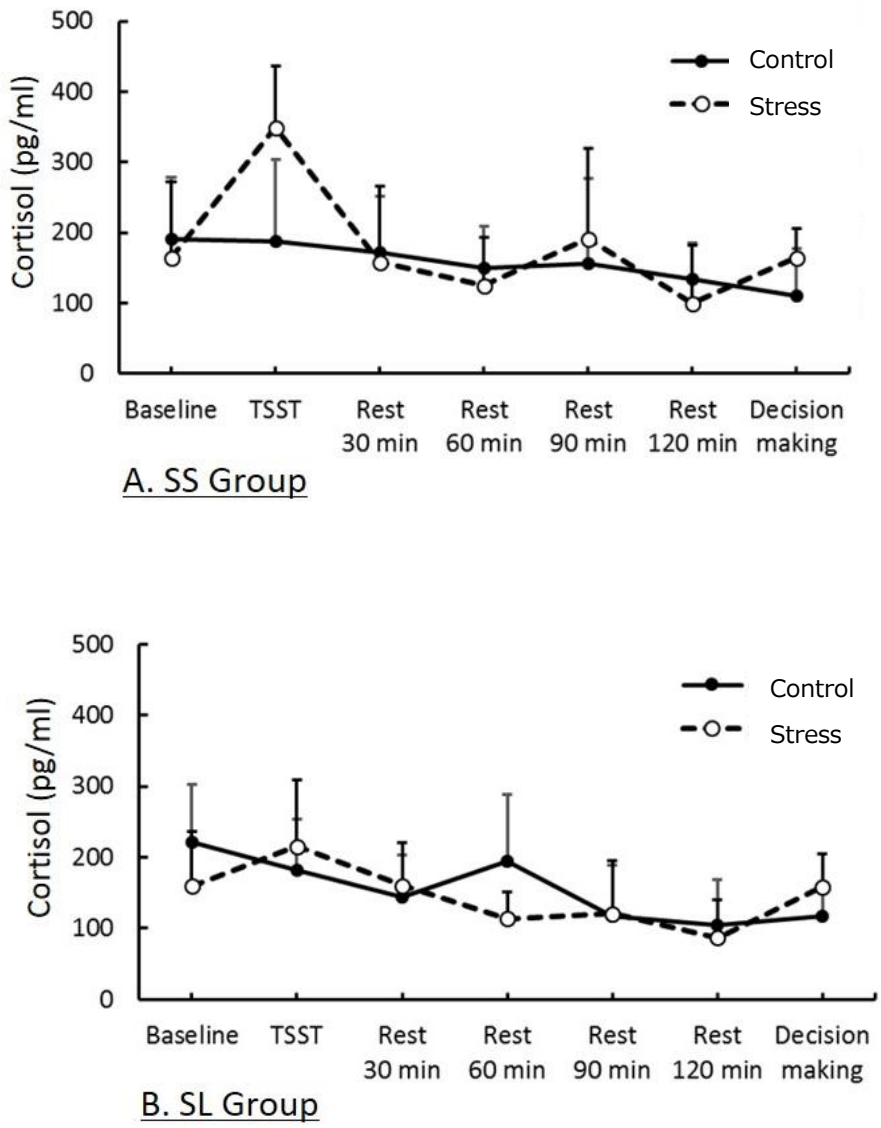

Figure 3.3. Cortisol concentration in each group and genotype.

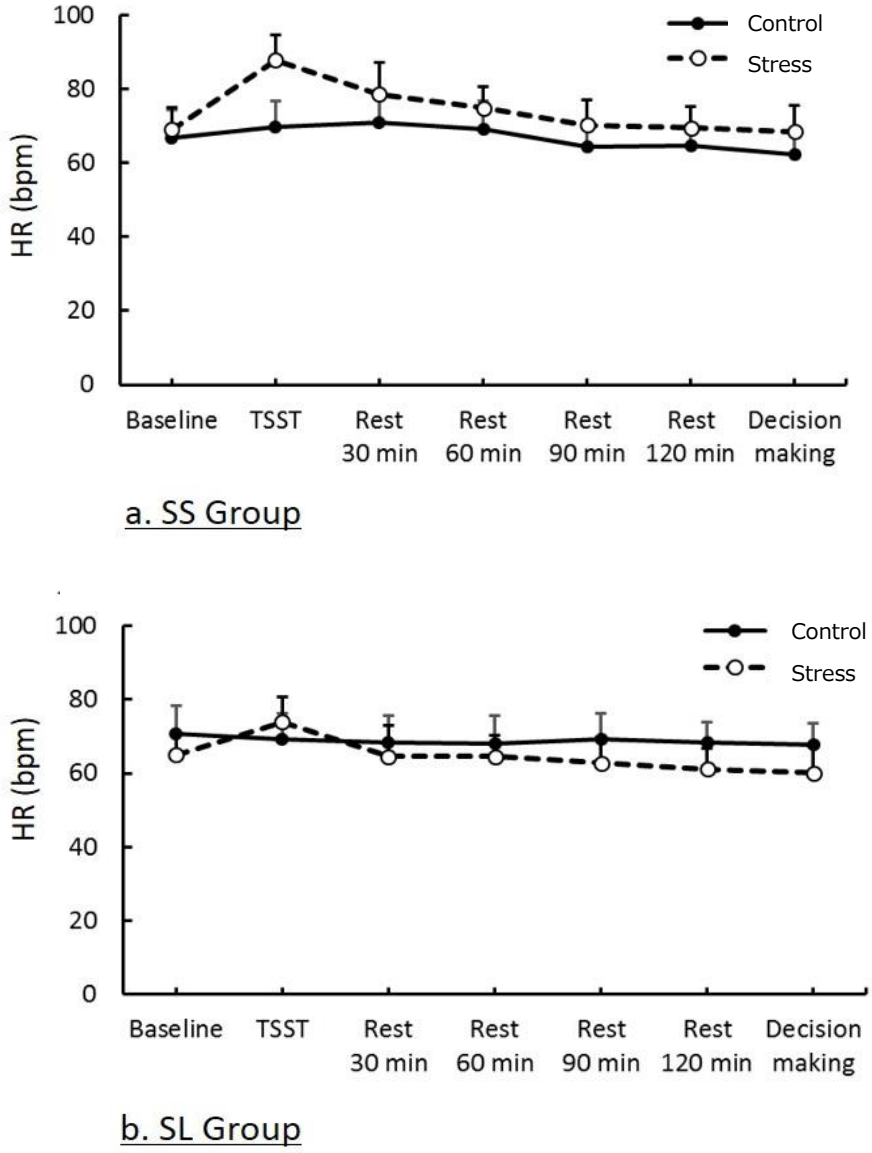

Figure 3.4. HR through experimental sessions in each group and genotype.

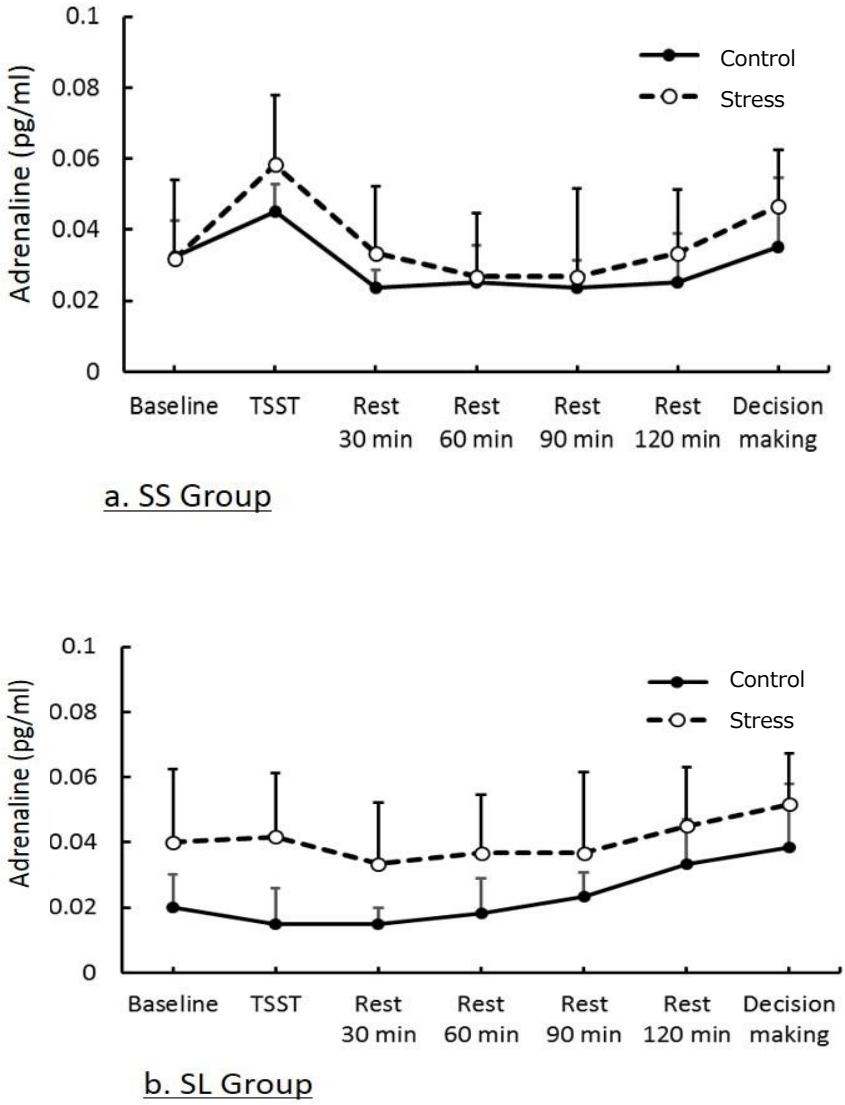

Figure 3.5. Adrenaline concentration in each group and genotype.

3.3.2 Stress effects on decision-making

3.3.2.1 Gamble choice

The rates of gamble choice in experimental conditions are shown in Figure 3.6. There was a significant interaction between Group, Domain, and EV level ($F(2, 44) = 4.56$, $p < 0.05$, $\eta_p^2 = 0.17$). Post hoc comparisons ($p < 0.05$) revealed that the rate of gamble choice in the Equal EV level for the Gain domain in the Stress group was smaller than that in the Control group. No effects of Genotype reached significance ($F(2, 44) = 1.23$, *n.s.* $\eta_p^2 = 0.05$).

3.3.2.2 Cardiac responses to gamble outcomes in decision-making

The means of magnitudes of HR deceleration from baseline (HR values for 1 second preceeding feedback onset; see 3.2.6.) are summarized in Figure 3.7a. An rmANOVA for magnitudes of HR deceleration revealed a significant interaction between Group, Domain, and EV ($F(1.30, 28.62) = 4.13$, $p < 0.05$, $\eta_p^2 = 0.16$). Post

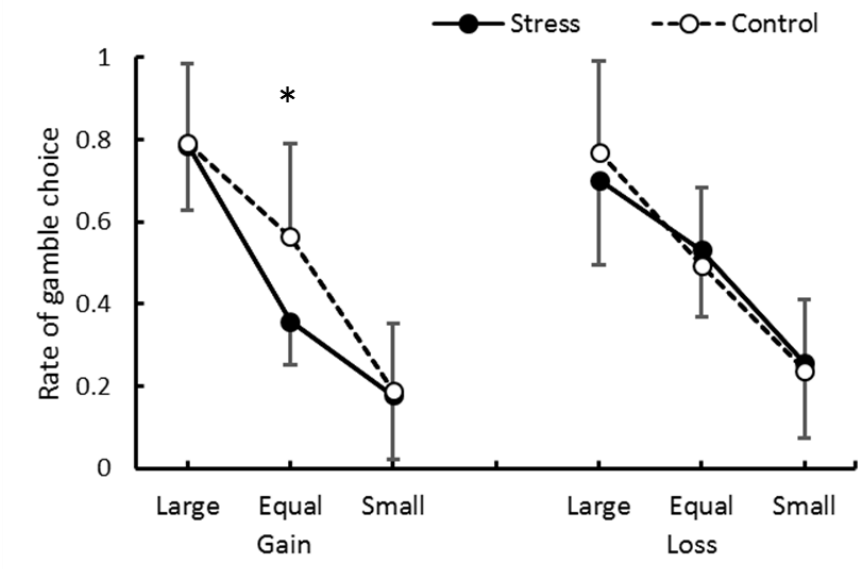

Figure 3.6. Rates of gamble choice.

hoc comparisons ($p < 0.05$) revealed that HR in the Equal EV level for the Gain domain in the Stress group was more decelerated than that in the Control group. As shown in Figure 3.7b, HR time-locked to the outcomes of gamble in the Equal EV level showed deceleration that can be interpreted as a typical orienting response. In contrast to the choice of gamble option, HR deceleration to the outcome of a keep option was less than that to the outcome of a gamble option ($p < 0.01$), and no difference was shown between groups (see Figure 3.9c). No effects of Genotype reached significance (F (1.30, 28.62) = 0.28, *n.s.* $\eta_p^2 = 0.01$).

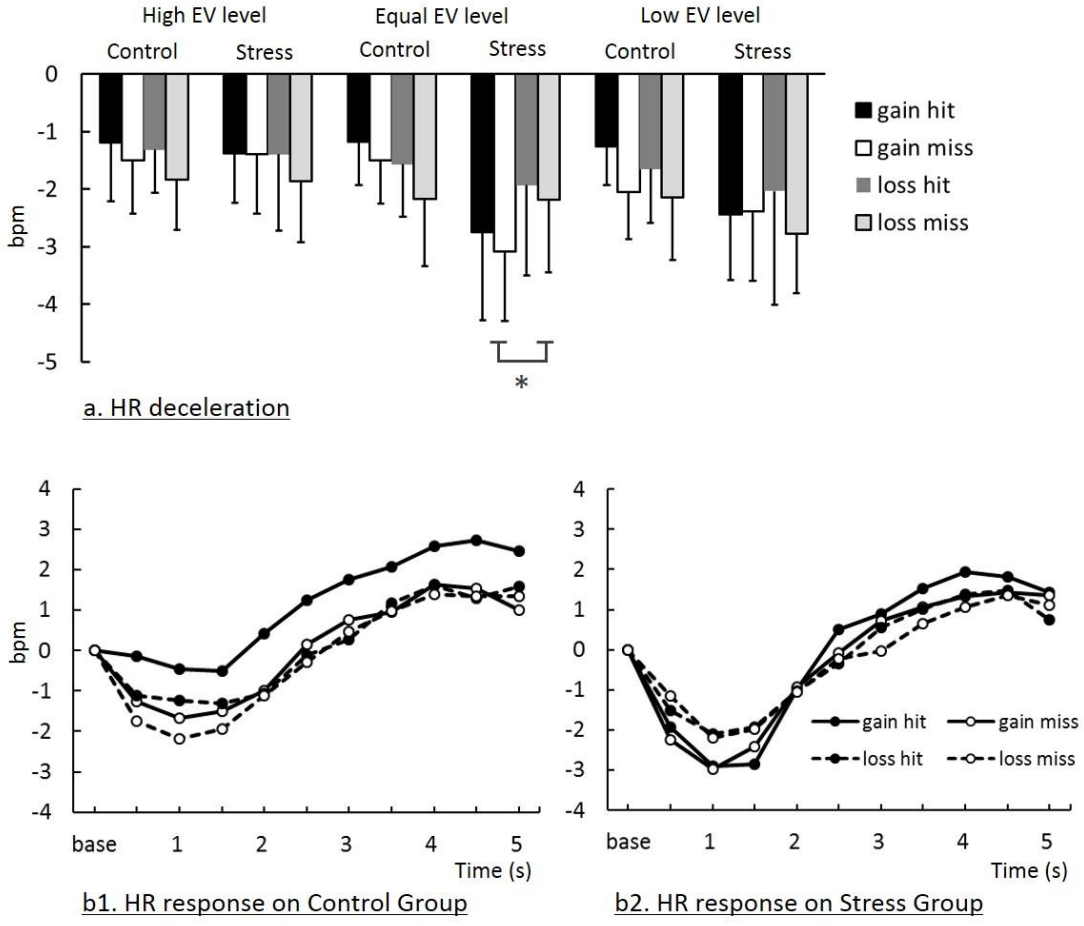

Figure 3.7. (a) HR deceleration in decision-making task. (b) Waveforms of time-series variations of HR deceleration.

There was no correlation between the rate of gamble choice and HR deceleration during decision-making periods (r = -0.23, *n.s.*). Therefore, HR deceleration reflecting trial-by-trial attention to decision-making outcomes did not influence the rate of gamble choice, contrary to the experiential account. Because this result indicated that gamble choice and HR deceleration are independent, I conducted further analyses of these variables separately, as explained in the following section.

3.3.3 Association between physiological parameters and decision-making

3.3.3.1 Hypothetical model

To examine the association between physiological responses caused by acute stress and later decision-making and to determine the influences of 5HTTLPR on the association, I conducted multiple-group SEM. I established the hypothetical models shown in Figure 3.8. As described above, because the HR deceleration did not affect the rates of gamble choice, these were treated as different dependent

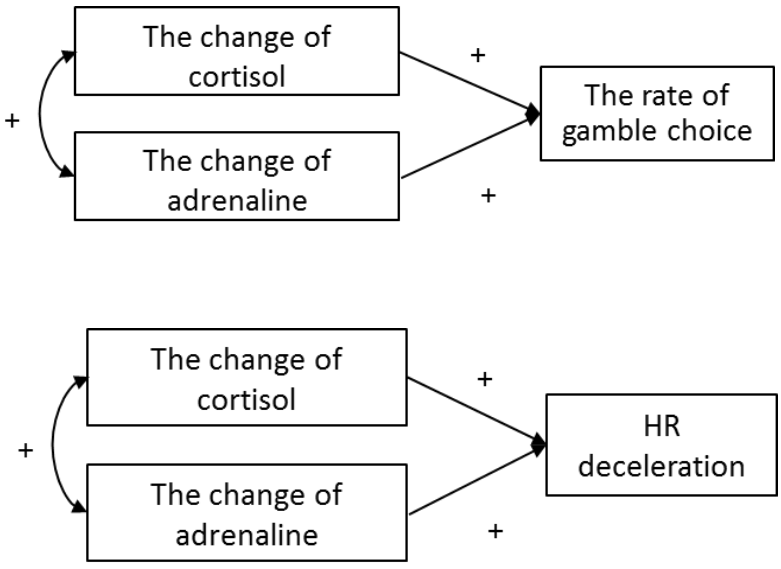

Figure 3.8. Hypothetical models for rates of gamble choice and HR deceleration.

variables and were analyzed separately. In this analysis, I focused on the Equal EV level condition at the Gain domain, where significant effects of acute stress on decision-making were observed. Magnitudes of HR deceleration to the hit and miss outcomes of gamble choices were averaged for each participant and were analyzed. Cortisol and adrenaline were used as predictors because previous studies reported that these indexes of the HPA and SAM system can affect risk-taking in decision-making and HR deceleration (Porcelli & Delgado, 2009; Putman, Hermans & van Honk, 2007). For cortisol and adrenaline, change values were calculated by subtracting the values at the baseline from the values immediately after the TSST, and those change values were used as predicted variables.

Because changes in cortisol and adrenaline levels are affected by 5HTTLPR genotypes (Ohira et al., 2009; Gotlib et al., 2008), multiple population analyses of SEM were conducted for rates of gamble choice and HR deceleration across 5HTTLPR genotypes.

3.3.3.2 Structural model

For the rate of gamble choice, I conducted two SEMs. The first SEM (Model 1) was conducted with the change of cortisol and adrenaline as the independent variables. A correlation between cortisol and adrenaline was allowed ($r = 0.72$, $p < 0.05$). As a result, a ratio chi-square/df = 6.45, GFI = 0.80 and RMSEA = 0.48 did not indicate an adequate overall fit. Therefore, on the basis that the prolonged effects of glucocorticoid on neural activity are stronger compared to adrenaline (Joëls et al., 2006), I modified the model by deleting a path from adrenaline to the rate of gamble choice (Model 2, Figure 3.9.). This model is valid from the significant correlation between changes in cortisol and the rate of gamble choice ($r = -0.91$, $p < 0.05$) and the non-significant correlation between changes in adrenaline and the rate of gamble choice ($r = -0.54$, *n.s.*) at the Gain domain for participants in the Stress group, including both the SS and SL genotypes (N = 12). Model 2 reached balance among statistical requirements and fit the data reasonably well, as indicated by multiple indicators of fit: ratio chi-square/df = 0.71, RMSEA = 0.00, and GFI = 0.96. To evaluate improvement of fit from Model 1 and Model 2, AIC

values (lower indicates a better fit) (Schermelleh-Engel et al., 2003) for the two models were compared. The value of the index decreased from 32.91 for Model 1 to 21.42 for Model 2.

Moreover, in Model 2, I observed a significant difference of associations among variables across 5HTTLPR genotypes. In the SS group, cortisol predicted the rate of gamble choice (β =–0.71, $p < 0.05$), whereas in the SL group, cortisol did not predict the rate of gamble choice ($\beta = 0.07$, *n.s.*). There was a significant difference in the prediction power of cortisol for the rate of gamble choice between the SS and SL groups ($zs > 1.96$, $p < 0.05$).

Likewise, I conducted two SEMs for HR deceleration. The first SEM (Model 3) was conducted using cortisol and adrenaline as independent variables. A correlation between cortisol and adrenaline was allowed; ratio chi-square/df = 6.45, GFI = 0.80, and RMSEA = 0.48 did not indicate an adequate overall fit. For a similar reason as that in the model of rate of gamble choice, I modified the model by deleting a path from adrenaline to HR deceleration (Model 4, Figure 3.10.). Model 4 fit the data reasonably well, as indicated by multiple indicators of fit: ratio chi-square/df = 1.96, RMSEA = 0.20, and GFI = 0.91. However, there were no significant path coefficients and differences across the 5HTTLPR genotype ($zs < 1.96$, *n.s.*). The AIC value comparing the improvement of fit strongly decreased from 32.91 for Model 3 to 23.92 for Model 4.

3.4 Discussion

Participants showed fewer risky choices in the gain domain 2 hours after exposure to acute stress, but no effect of acute stress on risky choices was observed in the loss domain. This result replicated a previous finding of domain-specific bias for risky decision-making (reflection effect: greater preference for cautious options in gains rather than in losses) observed immediately after exposure to acute stress (Pocelli & Delgado, 2009) and expanded it by showing that such an effect of acute stress can happen even later, when acute physiological stress responses in the HPA system and SAM system have disappeared. This

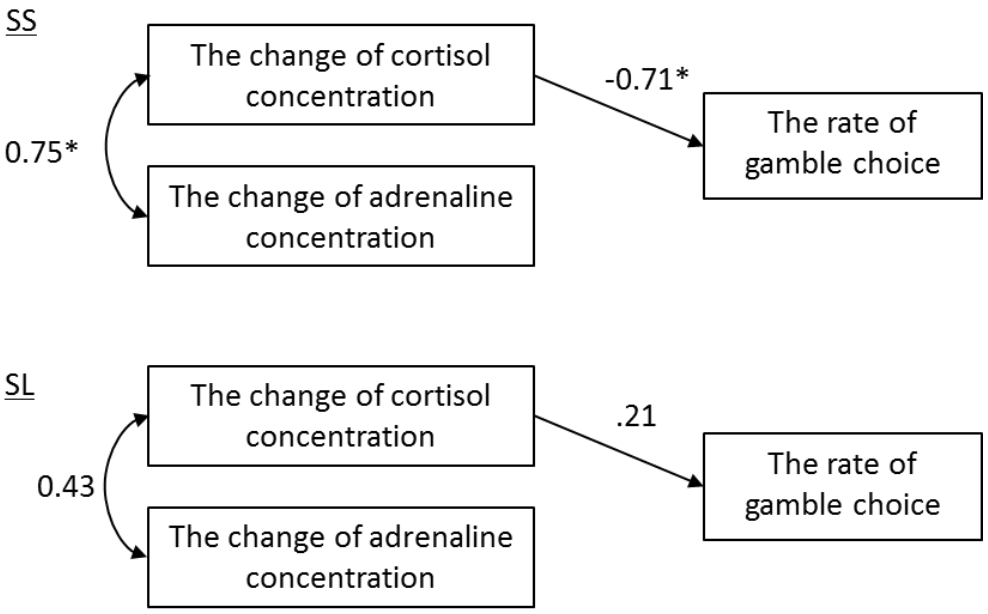

Figure 3.9. Structural model for rates of gamble choice.

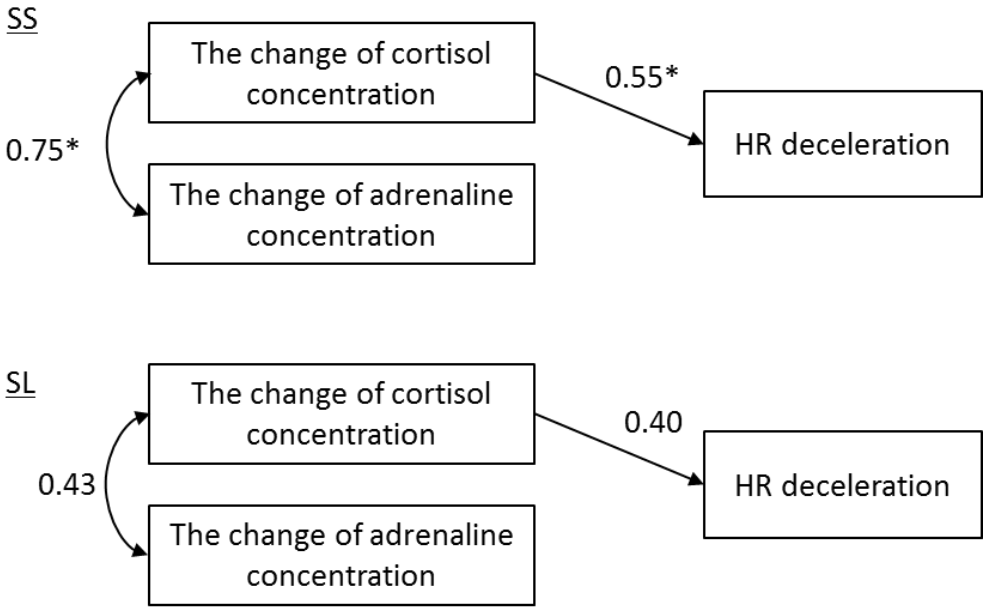

Figure 3.10. Structural model for HR deceleration.

stress-driven enhancement of preference for cautious options for gains was found only in a condition in which the EV of sure option and the EV of gamble option only in a condition in which the EV of sure option and the EV of gamble option were identical (Equal EV level); thus, a conflict of choice was the maximum. In conditions in which the EV of either option was greater, participants consistently made rational decisions based on the EV, and no influences of stress were observed. Therefore, it is difficult to attribute the greater preference on the Stress group for cautious gain options to the general impairment of cognitive functions caused by stress (McEwen & Sapolsky, 1995; Vedhara et al., 2000) or to a reduced motivation for monetary reward caused by stress (Ossewaarde et al., 2011). Thus, I suggest that currently observed results were not just artifacts and that acute stress can have substantially prolonged influences on decision-making. I also infer that this effect of acute stress on risk-taking might be based not on habitual action without deliberation, but on strategic, goal-directed action (Schwabe & Wolf, 2011).

Results of multiple-group structural equation modeling (SEM) indicated that 5HTTLPR genotypes affected prolonged effects of acute stress on risk avoidance. In participants with homozygous S alleles, the magnitude of cortisol reactivity to acute stress before 2 hours negatively determined the rate of risky-option choices for gains. In participants with heterozygous S and L alleles, however, cortisol reactivity to acute stress did not affect risky-option choices. This result is reasonable considering that individuals with homozygous S alleles consistently showed greater stress reactivity in cortisol secretion (Gotlib et al., 2008). Because rmANOVA showed no effects of the 5HTTLPR genotype on decision-making, 5HTTLPR likely does not directly regulate decision-making, but it does influence the association between physiological factors and decision-making. SEM results suggested that possible sources of individual differences in stress effects on decision-making are gene polymorphisms, including 5HTTLPR. In addition, SEM results suggested that the cautious shift in decision-making for gains two hours later was caused by cortisol reactivity of acute stress, at least partly. Because rapid responses to acute stress in the HPA system had ended and previously raised cortisol levels had returned to baseline when participants conducted the decision-

making task in this study, I infer the existence of some later effects of cortisol on the brain. As described here in the introduction, such prolonged effects of acute stress on neural activity of the amygdala and PFC (Henckens et al., 2010, 2011), in emotional memory (Diamond et al., 2007), in selective attention to emotional stimuli (Henckens et al., 2012), and in working memory (Henckens et al., 2011) have been clarified. These results can be interpreted in line with such previous studies.

Recent findings in human neuroimaging studies with pharmacological manipulations provided suggestions for domain specificity in effects of cortisol reactivity on risk avoidance observed in the present study. Participants who took hydrocortisone 105 min before they entered the MRI scanner showed reduced amygdala activity toward photographs of happy faces, but maintained amygdala activity toward those of fearful faces (Kukolja et al., 2008). Henckens et al. (2010) expanded this finding by demonstrating that the administration of a cortisol tablet (10 mg) first diminished the activity of the amygdala in response to happy and fearful faces, but activation to fearful faces returned to normal levels, whereas activation to happy faces was still dampened after 285 min post-administration. Such temporal characteristics of effects of cortisol on brain functions, particularly in the amygdala, involved in the reflection or framing effect (risk avoidance for gains and risk preference for losses) (De Martino et al., 2006) might lead to negativity bias in processing emotional information. The reduced reactivity of the amygdala to a gain might dampen impulsivity toward a large monetary reward. This phenomenon might lead participants to avoid the gamble option in the gain domain. Contrary to gains, the magnitude of amygdala reactivity to a loss might recover to normal levels during the decision-making task; therefore, typical risk preference in the loss domain might be maintained regardless of exposure to acute stress 2 hours before the task.

In the decision-making task, participants exposed to acute stress showed greater magnitudes of phasic HR deceleration just after a feedback signal than did participants who experienced no stress in the gain domain; in the loss domain, both groups indicated no differences in HR deceleration. This domain specificity in

prolonged effects of acute stress on HR responses was observed only when an EV of sure option and an EV of gamble option were equal. This result is consistent with the current result of risk avoidance in decision-making. HR deceleration following feedback can be interpreted as a sign of attentional orienting (Bradley, 2009; Osumi & Ohira, 2009) and monitoring (Hajcak, McDonald, & Simons, 2004) feedback; thus, this result suggests that risk avoidance in the gain domain in the Stress group was induced through deliberative processes accompanied by the enhancement of attention and monitoring, and not merely through a lack of cognitive resources or the abandonment of thinking caused by influences of stress. In addition, HR deceleration was consistently greater when participants chose a gamble option than when they chose a sure option in each condition in each group, suggesting heightened attention to outcomes of a gamble.

Notably, physiological responses, namely HR deceleration following feedback, did not directly affect decision-making. Thus, acute stress independently affected decision-making and HR responses. In addition, HR deceleration after feedback was sensitive only to domains (Gain vs. Loss) and not to outcomes (Hit vs. Miss). These findings can provide an important suggestion for whether effects of acute stress on decision-making are based on experiential processes or descriptive processes (Buckert et al., 2014). Lack of direct linkage between HR deceleration and risk avoidance and undifferentiated HR deceleration to Hit and Miss outcomes did not support the experiential account of stress effects on decision-making, in which reinforcement learning processes, according to online evaluations of positive and negative outcomes, are hypothesized. Present results are more consistent with the descriptive account, arguing that acute stress can affect decision-making through a top-down altering of representations for structures of decision-making. Results of multiple-group SEM, in which 5HTTLPR did not affect the association between physiological stress responses and HR deceleration, can be interpreted in line with this argument. Presumably, physiological stress reactivity governed by 5HTTLPR did not directly determine HR deceleration in decision-making but rather altered cognitive processes in decision-making. Then, HR deceleration was effected as an accompanying phenomenon. Therefore, in the Stress group, greater

HR deceleration in the gain domain should be a manifestation of enhanced attention on and monitoring of processes underlying decision-making under risk.

Chapter 4 Prolonged effects of glucocorticoid on psychological functions in decision-making under risk (Study 3)

4.1. Introduction

In Study 2 (Chapter 3), the following findings were obtained about the effects of acute stress on decision-making.

1. After exposure to temporarily distanced acute stress, the preference for a cautious option compared to a risky gamble was enhanced in a situation where monetary gains were delivered, but not in a situation where monetary losses were delivered.

2. The degree of this risk-avoidance tendency after acute stress was predicted by reactivity of cortisol to the acute stressor, suggesting the involvement via glucocorticoid system.

3. This risk-avoidance effect emerged only when an expected value (EV) of a cautious option and risky gamble were identical, suggesting that risk-avoidance effect might be controlled not by easy habit, but by deliberative goal-directed action.

4. The deceleration of heart rate (HR), which can be interpreted as a sign of attentional orienting and outcome monitoring was specifically observed in the condition where the risk-avoidance effect of decision-making appeared. This HR deceleration was independent from decision-making, suggesting that the risk-avoidance effect of decision-making might be mediated not by bottom-up processing based on trial-by-trial cognitive and affective experiences, which is caused by the outcomes of decision-making. It is, instead, caused by top-down processing based on alteration of cognitive description of values of options.

Here, one critical question about risk-avoidance tendency caused by acute stress remains unanswered. Did risk-avoidance tendency emerge by enhancing

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Data in Study 3 was provided in the 53rd Annual Meeting of Society for Psychophysiological Research (Florence Italy, 2013).

motivation to get a definite monetary gain, namely reward-seeing (stick to sure reward) or reducing attraction to a larger monetary gain that could be acquired through a risky gamble option, that is reward-avoidance (less commitment to larger reward)? To investigate this issue, in Study 3, I utilized an experimental protocol regarding reward processes modified paradigm of Pavlovian instrumental transfer (PIT; Lovibond, 1983). PIT is a phenomenon whereby a previously neutral stimulus (a conditional stimulus: CS) that has been linked with adaptively significant events, either positive or negative, (a reinforcer, or an unconditional stimulus: US) may exert control over instrumental actions (Kruse, Overmier, Konz, & Rokke, 1983; Trapold & Overmier, 1972). In this theoretical framework, such a previously neutral stimulus linked with US is usually called a "Pavlovian cue." Since present study did not perform manipulation check that a neutral stimulus evoked conditional response, the stimulus liked with stress response in present study was called a "stress-related cue" and phenomenon emerged by this manipulation was called PIT-like effect. I presented a neutral stimulus, cue (the color of the background of stimuli), for the decision-making task in Study 2 and linked the neutral stimulus with an option in a conventional stochastic learning task in Study 3. The stochastic learning task is an instrumental learning task where participants repeatedly choose an option to get monetary gains and avoid monetary losses. Contingencies between the options and outcomes (gains and losses) are usually stochastically manipulated, and participants have to decide based on what they learn about the contingencies. If participants would have motivation to obtain a reward caused by acute stress in Study 2, the stress-related cue would be affected by motivation and affect performances in stochastic learning task. One important thing is that this neutral stimulus is totally independent from the stimulus-outcome contingencies in the stochastic learning task. Thus, if participants' performances might be affected by the neutral stimulus, I can infer the effects that can reflect hidden tendency of reward-seeing caused in Study 2.

Some studies have examined the effects of stress on the PIT effects. In typical experimental procedures, PIT consists of three phases. In the first phase, a behavior [e.g., lever pressing for animals (Peciña, Schulkin, & Berridge, 2006)] or

grip squeezing for humans (Talmi, Seymour, Dayan & Dolan, 2008; Pool Brosch, Delplanque & Sander, 2015) is associated with a reward [e.g., food for animals (Peciña et al., 2006)], money (Talmi et al., 2008), and pleasant smells (Pool et al., 2015) for humans during initial instrumental conditioning. In the second phase, neutral stimuli [e.g., sounds (Peciña et al., 2006)] or geometrical figures (Talmi et al., 2008; Pool et al., 2015) are associated with the reward, CS or Pavlovian cue, during Pavlovian conditioning. Finally, animal subjects or human participants are exposed to a transfer test, where the Pavlovian cues are presented and their influences on instrumental actions (e.g., lever pressing or grip squeezing) are measured. When the effects of stress on the PIT are examined, it becomes clear that stressors are introduced in the period after the instrumental and Pavlovian conditioning and before the Pavlovian instrumental transfer test. Both for animals and humans, exposure to stress amplifies the size of the PIT effects (Peciña et al., 2006; Pool et al., 2015), suggesting that stress can motivate actions to obtain a reward later because of the presence of stress-related cues associated with the reward (for inconsistent findings, see Morgado, Silva, Sousa & Cerqueira., 2012; Pielock, Braun & Hauber, 2013).

However, this study aims to not examine the effects of stress on PIT by performance of PIT after acute stress but to estimate the inner state of participants due to specific enhancement or reduced motivation toward monetary rewards in decision-making tasks under risk. Previous studies reported the perception of inner state, which is called interoception, mediated emotion, cognition and behavior (Paulus, 2011; Smith & Lane, 2016). Interoception is sensing the physiological condition of the body and initiating motivation of action (Craig, 2002; 2007). One assumption is that perception of inner state stimulated by prior acute stress response modulate behavior, approach or avoidance. Therefore, I modified the experimental paradigm of PIT as follows and called PIT-like task. This study (Study 3) was planned and carried out a week or more after Study 2. In Study 2, participants were divided into a Stress group and a Control group to examine effects of stress on decision-making hours later. At this stage, I manipulated the cues (colors of background of the display where options for a choice were presented; blue or green) during the

decision-making task. In order to investigate whether the stress-related cues selectively influence reward-related decision-making, I established two groups at the stage of the stochastic learning task in Study 3, a Congruent group and an Incongruent group. In the stochastic learning task, participants chose one option from two alternatives to get monetary gains and avoid monetary losses. The expected value for the reward was higher for the advantageous option than for the other disadvantageous one. In the Congruent group, the stress-related cue was associated with the advantageous option. In contrast, in the Incongruent group, the stress-related cue was associated with the disadvantageous option. If participants had enhanced reward-seeing motivation caused by acute stress in the decision-making task in Study 2, the stress-related cue might be associated with the motivation. Thus, it was predicted that in the stochastic learning task in this experiment, the stress-related cue would boost choices of the advantageous option in the Congruent group more than in the Incongruent group. Alternatively, if participants had reduced motivation for the reward from the previous decision-making task, the effects of the stress-related cue would be reversed between the Congruent and Incongruent groups (less choices of the advantageous option in the Congruent group). To examine in more detail the behavioral processes which can underlie the effects of stress-related cues on decision-making, I adopted a computational model based on a conventional reinforcement learning algorithm—Q-learning model (Sutton & Barto, 1998).

In addition, in this study, I manipulated the degree of contingency between options and reward/punishment in the stochastic learning task. In the Contingent condition, an advantageous option led to monetary gain at a probability of 70% and led to monetary loss at a probability of 30%. Another disadvantageous option was associated with gain and loss at an invented probability (30% gain and 70% loss). In this condition, participants could easily establish predictions about the outcomes of their decision-making. In contrast, in the Random condition, the gain and loss rates were delivered randomly for both options (50% gain and 50% loss). In this condition, EVs were totally identical for any pattern of choices. This manipulation was introduced to examine whether the predicted effects of the stress-related cue

were mediated by goal-directed processing, or by habit processing. The goal-directed processing is sensitive to changes in the action–outcome contingency and motivational value of the outcome, and thus has a capacity to change behaviors rapidly and appropriately under uncertain environments. If the effects of the stress-related cue were via goal-directed processing, participants would be influenced by the stress-related cues when their choices could alter the probabilities of getting or losing the reward. In this situation, the stress-related cue would bias choices of options only in the Contingent condition, but not in the Random condition. In contrast, the habitual processing is insensitive to changes in the action–outcome contingency and motivational value of the outcome. If the effects in the stress-related cue on the stochastic learning task were via habit processing, participants would automatically be influenced by the stress-related cue, without the consideration of merits or demerits for the reward. In such a situation, the stress-related cue would bias choices of options in the same manner for both the Contingent and Random conditions. To consider the underlying mechanisms of the predicted effects from the stress-related cue on decision-making, the present study examines the association between the effects of the stress-related cue and physiological responses.

One of the possible biological factors underlying the promotion of effects from the stress-related cue is glucocorticoid. Recent studies have revealed that the promotion of neural activity mediated by glucocorticoid system can affect associations between sensory stimuli and motivational aspects of the reward. Peciña et al. (2006) indicated that the administration of corticotropin-releasing factor (CRF) into the shell of nucleus accumbens amplifies motivation for cued rewards, in particular, by magnifying incentive salience that is attributed to the Pavlovian cues previously associated with those rewards. This finding suggests involvement of the glucocorticoid system in the effects from the stress-related cue on decision-making. It is not clear whether other major biological stress system, namely the SAM system. This study explores possible influences of reactivity of cortisol and adrenaline to the prior acute stressor on the PIT-like effects for performance in the stochastic learning task. To achieve this objective, I conducted

analyses using a multiple-group structural equation modeling (SEM) with change scores for cortisol and adrenaline as independent variables and choices of options as the dependent variable. Because the reactivity of cortisol selectively predicted the magnitude of risk-avoidance in decision-making in Study 2, it was predicted that the reactivity of cortisol would also selectively predict the degree of effects from the stress-related cue and, thus, can affect choices of options in the stochastic learning task. If such a consistent result was observed, the plausibility of prolonged effects of stress on decision-making mediated via the glucocorticoid system would be more supported.

Moreover, the present study measured the transient deceleration of HR as an orienting response, which is a typical physiological response to feedback signals in decision-making. As discussed in Study 2, the phasic HR deceleration can be interpreted to indicate increased attention to a stimulus enhancing defensive or appetitive motivation (Sánchez-Navarro et al., 2006; Bradley et al., 2001). That is, whether the predicted effects from the stress-related cue on the choice of options occurs through experiential or descriptive processes. The stress-related cue might amplify responses to gain-and-loss feedback; therefore, it could bias future choices through learning processes (the experience account). In contrast, the stress-related cue might affect evaluations of the contingency between options and outcomes (gain/loss) and, thus, could bias choice behavior without learning processes (the description account). If the experiential account is correct, HR deceleration should correlate with the rate of choice of the advantageous option. If the description account is correct, HR deceleration is an accompanying response of top-down processing. In this case, HR deceleration would be rather independent from choice behaviors.

4.2 Methods

4.2.1 Participants

The participants in Study 2 (Chapter 3) were 28 Japanese male undergraduates of Nagoya University, in the age range of 18–22 years old (mean = 19.92; S.D. = 1.20) who also took part in this study. They were randomly assigned to either a Stress group (N = 14) or to a Control group (N = 12). Two participants in the Control group were excluded from the analysis because of technical problems in data collection. None of the participants suffered from any chronic illnesses nor were taking any medications. The participants were advised not to smoke or drink alcohol during the day they participated in the experiments. All participants signed an informed consent to participate in the study in accordance with the guidance of the ethics committee of Nagoya University.

4.2.2 Procedure and stochastic learning tasks

Participants were further divided into a Congruent group (N = 5 in Stress group; N = 7 in Control group) and an Incongruent group (N = 7 in Stress group; N = 7 in Control group). All participants took part in this experiment about one week after the experimental session of Study 2 (Chapter 3). Electrodes for electrocardiographic measurement were attached to the inner side of the left leg and the inner side of the non-dominant forearm of each participant. Cardiac activity was measured continuously throughout the experimental session. Instruction for the stochastic learning task was given and participants conducted the task after a number of practice trials.

Participants performed four blocks of a stochastic learning task, two blocks of a contingent condition, and two blocks of a random condition. Each block contained 40 trials. In each trial, participants were presented with two abstract line drawings on the left and right sides of a fixed stimulus and were required to choose one by pressing a key within the time frame for the presentation of the stimuli. The stimuli were selected from the set of Novel Shapes, which were validated on evaluating the

level of verbalization association and simplicity (Endo, Saiki & Saito, 2001). The merit of using such abstract stimuli is to prevent participants from verbal coding and from forming easy memory strategies (Ohira et al., 2010). After the termination of presentation of the stimuli, a feedback signal indicting reward (gain of 100 Japanese Yen (JPY) or punishment (loss of 100 JPY) was displayed (Figure 4.1). If participants did not choose a stimulus within 1,000 ms, they lost on that trial. In this task, the probability of reward and punishment associated with both stimuli was manipulated. In a Contingent condition, one stimulus was associated with reward at a probability of 70% and punishment at a probability of 30% (advantageous stimulus). The other stimulus was associated with reward at a probability of 30% and punishment at a probability of 70% (disadvantageous stimulus). To examine the predicted effects from the stress-related cue that were assumed to be evoked by prior acute stress on later decision-making, I manipulated the color of the background for each stimulus. Two stimuli for the stochastic

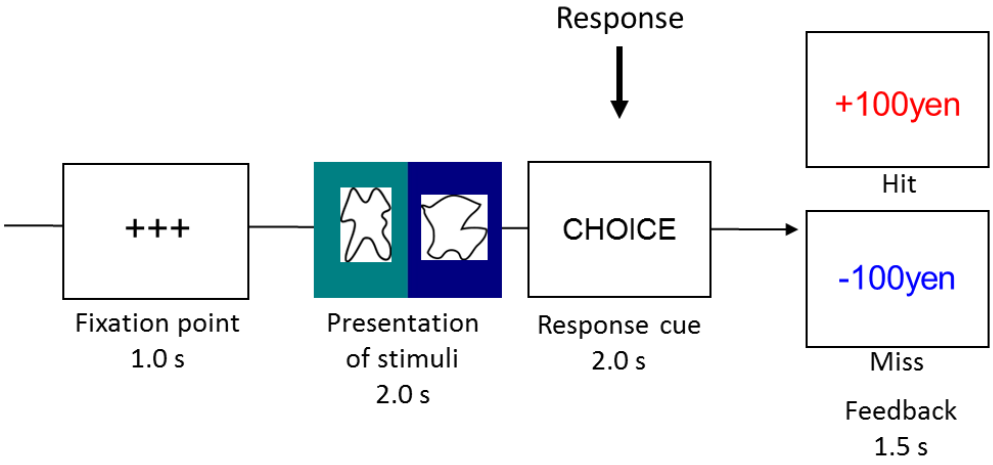


Figure 4.1. Decision-making task.

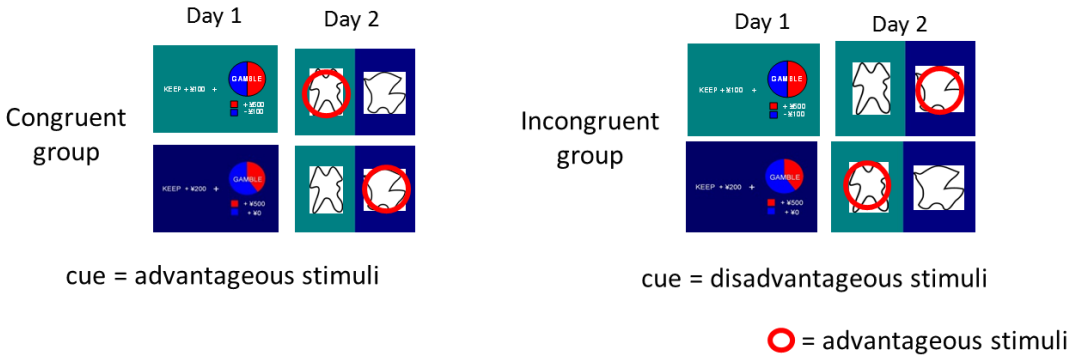


Figure 4.2. The relationship between advantageous stimuli and stress-related cue in each group.

learning task were presented on the background with different colors, respectively (blue or green: Figure 4.2). These colors had been previously used as the background in the previous gambling choice task (Study 2), for both the Congruent and Incongruent groups. The color of the background for the advantageous stimulus in the Congruent group was identical to the color presented as the background in the previous gambling choice task. In contrast, the color of the background for the disadvantageous stimulus for the Incongruent group was identical to the color presented in the gambling choice task. Therefore, the colors used for the background in the gambling choice task defined the stress-related cue, which was associated with the level of stress response. I counterbalanced the two colors (blue or green) for the advantageous or disadvantageous stimuli between the participants.

On the other hand, in a Random condition, both stimuli were rewarded or punished with a 50% probability rate, so the advantageous stimulus was operationally defined as a stimulus selected at random. Also, in the Random condition, the colors of the background as stress-related cues were manipulated in the same manner as in the Contingent condition. All participants performed both conditions and the order of the two conditions was counterbalanced between the participants. At the end of the procedure, the electrodes were removed, the participants were fully debriefed, and they were thanked for their participation.

4.2.3 Behavioral measures and reinforcement learning model

In the Contingent condition, I measured response bias, defined as the rate of selection of the advantageous stimulus in each of 20 trials. In the Random condition, the response bias was calculated as the rate of selection of the advantageous stimulus, which was operationally defined as described above, in each of the 20 trials.

For the trial-based analysis of the learning process, I adopted a Q-learning model, a standard reinforcement learning model that updates action values based on the Rescola-Wagner model (Rescorla & Wagner, 1972). This model represents the selection of one option as Q-values. Let $Q_{a(t)}$ (t) refer the Q-value for option (t)(a(t) = 1,2) in trial t. The Q-values are updated using by the action and outcome. Let a(t) (=1, 2) refer the option chosen in trial t. The Q-value corresponding to the selected target is updated as follows:

$$Q_{(a(t))}(t+1) = Q_{a(t)}(t) + \alpha\,(R(t) - Q_{a(t)}(t)), \qquad (1)$$

where the Q-value corresponding to the unselected target does not change. The learning rate is α that determines the degree of the update. $R(t)$ is the reward value of the choice during trial t. $R(t)$ is equal to one if the reward is provided and is equal to zero (0) if punishment is provided.

Given a Q-value set, a choice is made by the soft-max function, where the probability of choosing option 1 is as follows:

$$P(a(t) = 1) = \frac{1}{1+\exp[-\beta\,(Q_1(t) - Q_2(t))]}, \qquad (2)$$

where $P(a(t) = 2) = 1 - P(a(t) = 1)$. Here, β is the degree of stochasticity in making the choice. I estimated the learning rate (α) as an index of modulation of the reward prediction error in each trial.

4.2.4 Cardiovascular measurement

Cardiodynamic activity was recorded using an electrocardiogram (ECG) at a sampling rate of 500 Hz using the MP 100 system (Biopac Systems Inc., CA, USA) and Ag/AgCL electrodes on the extremities. The analysis of ECG waveforms was performed using AcqKnowledge software for MP 100. For the analysis of cardiac data in the decision-making task, inter-beat intervals were obtained from deviations between R-waves and converted into beats per minute (bpm) after the rejection of artifacts in the ECG waveforms. HR in bpm was averaged in half-second intervals and deviated from the 1 sec baseline preceding the feedback onset. Initial deceleration was assessed as the minimum value in the 0–3 sec of the feedback presentation period in each trial. It is known that HR deceleration reflects a sign of attentional orientiation governed by parasympathetic activity (Bradley 2009; Osumi & Ohira 2009). For this reason, I focused on this measure in order to examine outcome-related activity induced by feedback signals indicating Reward and Punishment.

4.2.5 Experimental design and statistical analysis

For response bias, I divided two blocks of a condition (40 trials x 2 blocks) into four periods of twenty trials to examine learning processes in detail. Data from the response bias were administered for 2 (Exposure: Stress vs. Control) x 2 (Congruency: Congruent vs. Incongruent) x 4 (Period: 1-1 block, 1-2 block, 2-1 block, and 2-2 block) x 2 (Condition: Contingent vs. Random) repeated-measures analyses of variance (rmANOVA). Exposure and Congruency were between-participant factors and Period and Condition were within-participant factors. Parameters of Q-learning [learning rate (α) and exploration parameter (β)] were administrated for 2 (Exposure: Stress vs. Control) x 2 (Congruency: Congruent vs. Incongruent) x 2 (Condition: Contingent vs. Random) rmANOVA.

Cardiac data for feedback in the decision-making task were analyzed using a 2 (Exposure: Stress vs. Control) x 2 (Congruency: Congruent vs. Incongruent) x 2 (Condition: Contingent vs. Random) x 2 (Outcome: Reward vs. Punishment)

rmANOVA. Exposure and Congruency were between-participant factors and Condition and Outcome were within-participant factors. The sphericity assumption of errors was tested by Mauchly's sphericity test. If the assumption was not sufficient, the Greenhouse–Geisser epsilon correction factor, ε (Jennings & Wood, 1976), was used to modify the degree of freedom for the F-test. In cases where significant interactions were found, post hoc analyzes using Bonferroni tests ($p < .05$) were conducted to examine which combinations of data points differed significantly. Effect sizes are presented as η^2-values.

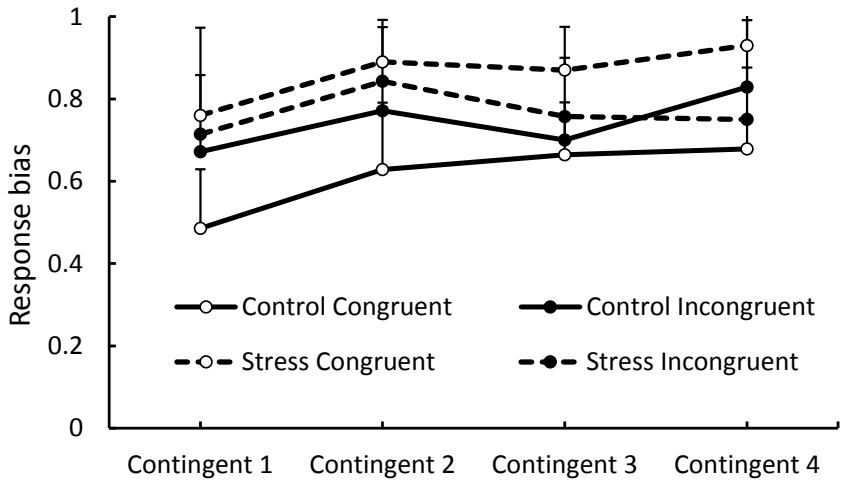
To examine the manifestation of effects of prior physiological stress responses as effects in stress-related cues on later decision-making, I performed exploratory analysis. Multiple-group structural equation modeling (SEM) was conducted using physiological parameters as predictors for response bias in decision-making across Congruency. Considering the sample size of the present study, the overall model fit was assessed using a chi-square/degree of freedom (df) ratio, goodness-of-fit index (GFI), and root mean square error of approximation (RMSEA). A chi-square/df ratio ≤ 0.20, a GFI ≥ 0.95, and an RMSEA ≤ 0.05 are considered the standard of a good fit (Schermelleh-Engel et al., 2003).

4.3 Results

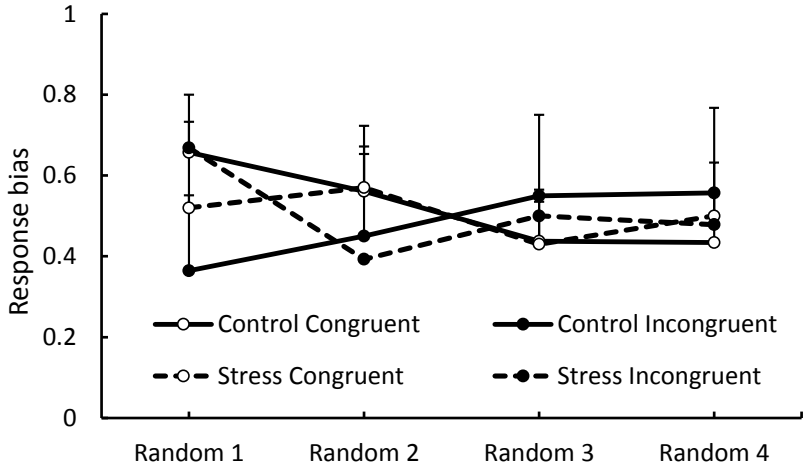
4.3.1 Behavioral measures

Changes of the response bias are presented in Figure 4.3. There was a significant interaction between Exposure, Congruency, Period, and Condition ($F(2.20, 48.33) = 3.72$, $p < 0.05$, $\eta_p^2 = 0.14$). Post hoc comparisons ($p < 0.05$) revealed that the response bias in the Congruent group for the Contingent condition in the Stress group was larger than that in the Control group.

Results of the learning rate are shown in Figure 4.4. Main effects of Exposure and Condition were statistically significant ($F(1, 22) = 6.52$, $p < 0.05$, $\eta_p^2 = 0.23$; $F(1, 22) = 7.50$, $p < .05$, $\eta_p^2 = 0.25$). Furthermore, a tendency of interaction between



a. Contingent condition



b. Random condition

Figure 4.3. Response bias.

Exposure and Congruency was found ($F(1, 22) = 4.10$, $p < .10$, $\eta_p^2 = 0.16$). Post hoc comparisons ($p < 0.05$) revealed that the learning rate in the Congruent group and Stress group was larger than that in the Control group. However, no interaction among Exposure, Congruency, and Condition reached significance ($F(1, 22) = 0.32$, *n.s.* $\eta_p^2 = 0.01$). For the exploration parameter, there were neither significant main effects nor interactions ($F(1, 22)$ =0.26-0.53, *n.s.*, $\eta_p^2 = 0.01$-0.04).

4.3.2 Cardiac responses

Means of magnitudes of HR deceleration from the baseline (HR values for one (1) second preceeding feedback onset) are summarized in Figure 4.5a. An rmANOVA for magnitudes of HR deceleration revealed a significant main effect for Outcome ($F(1, 22) = 68.67$, $p < 0.05$, $\eta_p^2 = 0.66$). There was a significant interaction between Exposure and Congruency (F (1, 22) = 5.89, p < .05, η_p^2 = 0.21). Post hoc comparisons ($p < .05$) revealed that HR in the Congruent and Stress group was

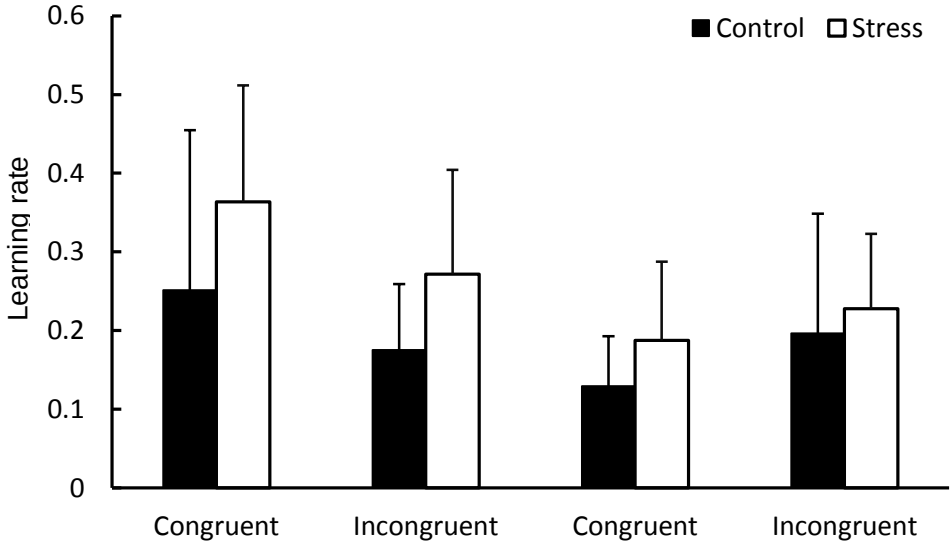
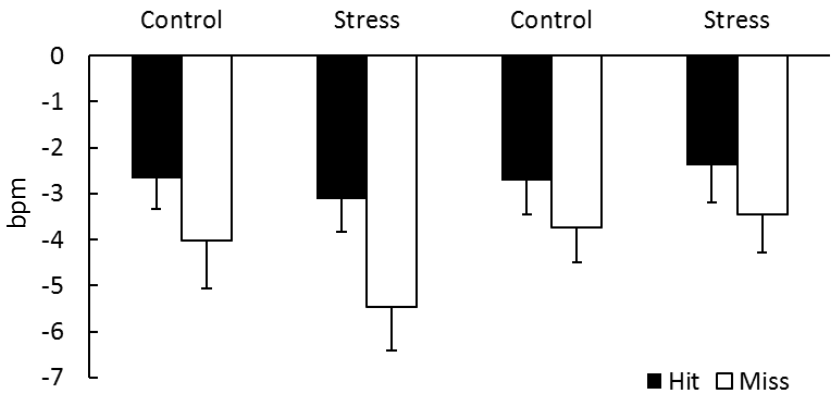
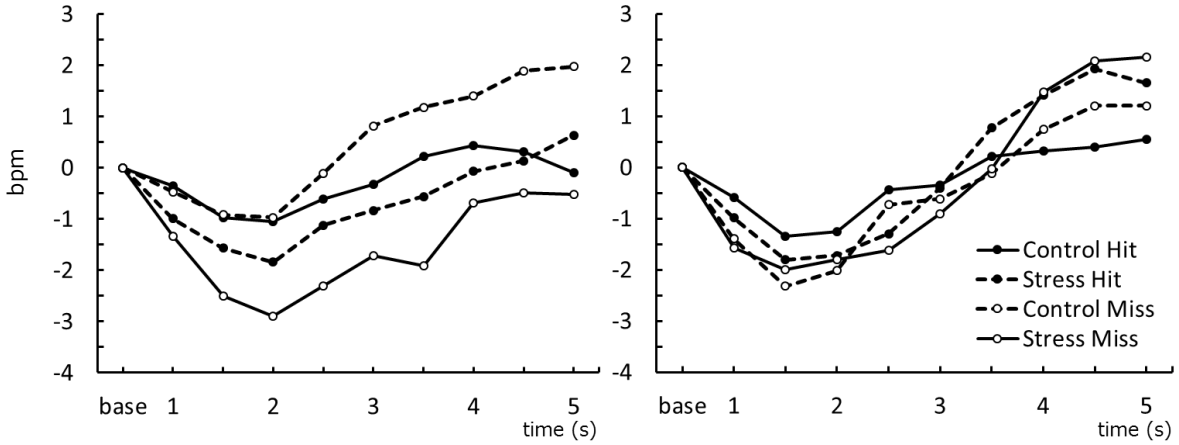


Figure 4.4. Learning rate.

more decelerated than that in the Congruent and Control group. As shown in Figure 4.5b, HR time-locked to the outcomes showed deceleration that can be interpreted as a typical orienting response. Furthermore, althogh an interaction among Exposure, Congruency, and Condition did not reach significance



a. HR deceleration



b1. HR response in congruent group

b2. HR response in incongruent group

Figure 4.5. HR response to the presence of feedback.

($F(1, 22) = 0.37$, *n.s.*, $\eta_p^2 = 0.02$), post hoc comparesons ($p < 0.05$) revealed that HR in the Contingent condition in the Congruent and Stress group was more decerelerated than that in the Control group.

There was also no correlation between the behavioral measures (response bias, learning rate, and exploration parameter) and HR deceleration (r = -0.11 – 0.24, *n.s.*). Therefore, HR deceleration, reflecting trial-by-trial attention to outcomes of decision-making, did not influence behaviors. This result indicated that behavioral aspects of decision-making and HR deceleration are independent. Therefore, I analyzed determinants of these indices separately, as described in the following section.

4.3.3 Association between physiological responses and decision-making

4.3.3.1 Hypothetical model

To examine causal relationships between physiological stress responses and aspects of later decision-making, I conducted multiple-group SEM. I established hypothetical models as illustrated in Figure 4.6. In this analysis, I focused on the Contingent condition, where significant effects of acute stress on response bias were observed. The response bias did not correlate with behavioral indices of the previous gambling choice task (Study 2), such as the rate of choice (r = - 0.25, *n.s.*), suggesting that experiences of success or failure, and accompanying good or bad effective states presumably did not work as stress-related cues in the stochastic learning task. In addition, the response bias did not correlate with parameters in the reinforcement learning model, such as learning rate (r = 0.27, *n.s.*), or with HR deceleration during the stochastic learning task (r = -0.11, *n.s.*). These results suggested that behavioral and physiological characteristics did not seem to determine the response bias. On the basis of these observations, the reactivity of cortisol and adrenaline in the prior acute stress task were chosen as possible predictors because previous studies reported that these indices of the HPA system and SAM system can affect reward preference and learning parameters in decision-making (Schwabe & Wolf, 2011, Cerquerira, Pêgo, Taipa, Bessa, Almeida & Sousa,

2005). For cortisol and adrenaline, change values were calculated by subtracting the values at the baseline from the values immediately after the TSST, and those change values were used as prediction variables. For comparison of the effects by presentation of the stress-related cue, multiple population analyses of SEM were conducted for response bias across the Congruent and Incongruent groups.

3.3.3.2 Structural model

For the response bias, I conducted two SEMs. The first SEM (Model 1) was conducted with changes of cortisol and adrenaline as independent variables. A correlation between cortisol and adrenaline was allowed ($r = 0.72$, $p < 0.05$). As a result, a ratio chi-square/df = 8.82, RMSEA = 0.57, and GFI = 0.77 did not indicate an adequate overall fit. Therefore, on the basis that the prolonged effects of

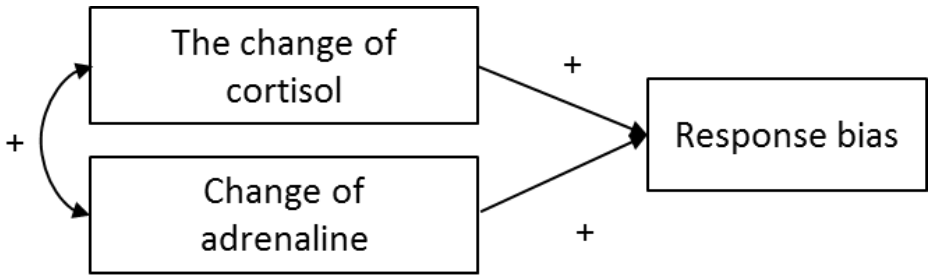


Figure 4.6. Hypothetical models for response bias.

glucocorticoid on neural activity are stronger in comparison to adrenaline effects (de Kloet, 2008), I modified the model by deleting a path from adrenaline to the response bias. Though statistical requirements for model 2 (Figure 4.7.) were not sufficient enough, as indicated by multiple indicators of fit: ratio chi-square/df = 2.63, RMSEA = 0.26, and GFI = 0.89, AIC values (lower indicates a better fit) deceased from 37.64 for Model 1 to 25.26 for Model 2. It means Model 2 fit the data better than Model 1.

Moreover, in Model 2, I observed a significant difference in associations among variables across the Congruent and Incongruent groups. In the Congruent group, cortisol predicted the response bias ($\beta = 0.56$, $p < 0.05$), whereas in the Incongruent

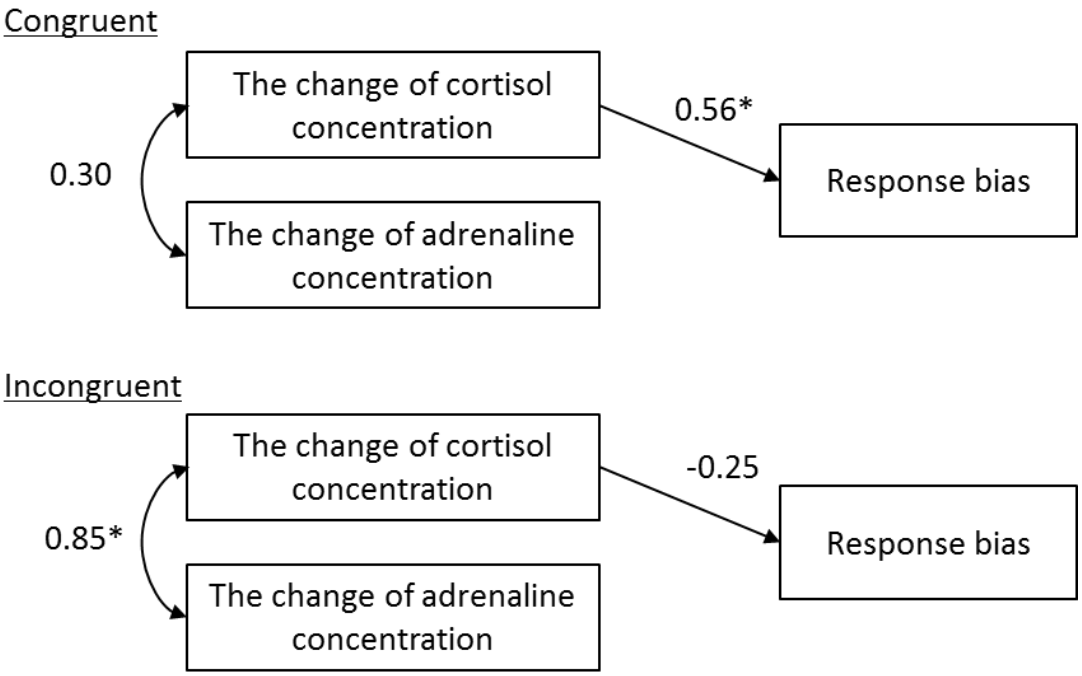


Figure 4.7. Structural model for response bias.

group, cortisol did not predict the response bias (β = -0.25, *n.s.*). There was a significant difference in the prediction power of cortisol for the response bias between the Congruent and Incongruent groups ($zs > 1.96$, $p < 0.05$).

Likewise, I conducted two SEMs for HR deceleration. The first SEM (Model 3) was conducted using cortisol and adrenaline as independent variables. A correlation between cortisol and adrenaline was allowed; ratio chi-square/df = 8.82, GFI = 0.77, and RMSEA = 0.57 did not indicate an adequate overall fit. For a similar reason as in the model for response bias, I modified the model by deleting a path from adrenaline to HR deceleration (Model 4). Model 4 fit the data, as indicated by multiple indicators of fit: ratio chi-square/df = 0.17, RMSEA = 0.00, and GFI = 0.99. However, in the Congruent and Incongruent group, cortisol did not predict the response bias (β = -0.10–0.04, *n.s.*).

4.4 Discussion

This study primarily aimed to investigate whether inner states of participants, which are affected by prior acute stress responses, specifically enhanced or reduced motivation for the monetary reward available in a decision-making task with associated risk in Study 2. Using a PIT-like experimental paradigm, where a previously neutral stimulus (the color of the background of the display) was presented in the decision-making task in Study 2, and its influences on the choices of options in a stochastic learning task in Study 3 were examined. As a result, prior acute stress was shown to enhance the effects of the stress-related cue and amplify the rate of choice of an advantageous option, selectively in the Congruent group, where the stress-related cue was associated with the advantageous option. This result was caused by a process whereby the stress-related cue enhanced the learning rate in reinforcement learning in the Congruent group, compared to that in the Incongruent group. These results suggest that the enhancement of preference for a cautious option shown in Study 2 was caused by the promotion of motivation to obtain a reward. These results and interpretations are consistent with findings in previous studies that stress can increase reward

pursuits (Lighthall, Gorlick, Schoeke, Frank & Mather, 2013; Pool et al., 2015).

The second purpose of this study was to examine whether the predicted effects of the stress-related cue is mediated by goal-directed processing with a sensitive contingency or habit processing with insensitive that. For this purpose, I manipulated the degree of contingency between options and outcomes (gains/losses) in stochastic learning. It was demonstrated that participants' decision-making was influenced by the stress-related cue only when their choices could alter the probabilities of getting the reward (the Contingent condition), but not when their decision-making could not affect the probabilities of getting the reward (the Random condition). These results indicated that the presentation of stress-related stimulus enhanced the sensitivity to contingency. Sensitivity to the contingency between actions and reward is shown to be a key of goal-directed processing in rats (Balleine & Dickinson, 1998). Therefore, it is possible that the prolonged effects emerged goal-directed processing through the stimulus related stress response. Recent evidences suggested that medial prefrontal cortex (mPFC), which is region in the on-line computation of contingency, monitored changes in relationship between action and outcome and controlled goal-directed processing (Tanaka, Balleine, & O'Doherty, 2008). Present result suggests that the effects of the stress-related cue were mediated by goal-directed processing rather than habit processing. This result is consistent with the report of Joëls, Sarabdjitsingh & Karst (2012) that stress can enhance prefrontal cortical function which plays a critical role in improving decision-making to obtain a reward. The influence of food-related cues on goal-directed behavior to obtain food was especially evident in situations where participants were hungry (Perks & Clifton, 1997), suggesting significance of such effects for adaptation. The results in this study support an inference that acute stress can promote adaptive behaviors by enhancing goal-directed processing.

A previous study clarified that the administration of CRF, which activates stress-related glucocorticoid reactivity into the nucleus accumbens (NAcc), amplifies positive motivation for rewards associated with a Pavlovian cue (Peciña et al., 2006). However, in Study 2, it was observed that the prolonged response of

acute stress led to risk-aversion in decision-making, whereas previous studies revealed that activity in the striatum, including the NAcc, promotes risk-taking behaviors (Preuschoff, Bossaerts & Quartz, 2006). Therefore, it does not seem that activation of the NAcc through prolonged glucocorticoid responses caused effects in cases where there had been prior acute stress. In a previous study for prolonged glucocorticoid responses, promoted LTP in the PFC (Henckens et al., 2011) via alteration of functions in glucocorticoid receptors has been clarified. The areas of the PFC that support information integration are necessary for choices of optimal options (Kennerley & Walton, 2011; Chase 2015). These results can be interpreted as aligning with such previous studies. Put together, the effects of prior acute stress observed in this study should be attributed to activation of the PFC modulated by the prolonged glucocorticoid responses. However, because of the lack of neural data in this study, this interpretation is just speculative and has to be certificated in future studies.

The results of multiple-group SEM suggested that even though statistical requirements were insufficient, the effects in stress-related cues in this study was determined by responses of cortisol immediately after exposure to acute stress. The response bias in the Contingent condition was positively determined by the magnitude of cortisol reactivity to acute stress in the Congruent group, but cortisol reactivity to acute stress did not affect the choice of an alternative linked with the stress-related cue in the Incongruent group. This study manipulated the stress-related cue presented in the decision-making task two hours after exposure to acute stress when elevated prolonged glucocorticoid reactivity was assumed. As described above, prolonged effects of acute stress can cause powerful influences on emotional and cognitive functions (Henckens et al., 2012) despite the disappearance of acute physiological stress responses. Along with the results of Study 2, this association between cortisol reactivity and the magnitude of the effects from the stress-related further implies that the prolonged effects of acute stress on decision-making might be mediated mainly by responses in the glucocorticoid system.

Performances of decision-making tasks such as the rate of choice of the risky gambling option and the amount of acquired monetary reward in Study 2 did not

affect the response bias or learning rate in the stochastic learning task in Study 3 at all. Only cortisol reactivity affected the response bias as described above. This result is very important considering that the stress-related cue can be theoretically associated with any parameter, for example the rates of gamble choice, during the decision-making task in Study 2. The selective association between cortisol reactivity and the PIT-like effects suggests that the stress-related cue was associated with inner states of participants caused by glucocorticoid response, but not with other items and factors that participants experienced during the decision-making task. This implication is critical for the explanation of underlying mechanisms of the prolonged effects of acute stress on decision-making.

Participants in the Stress and Congruent groups showed greater magnitudes of phasic HR deceleration in the Contingent condition just after a feedback signal in the stochastic learning task. As described in Study 2, HR deceleration following feedback of an outcome of decision-making can be interpreted as a sign of attentional orienting to outcomes (Baldley, 2009; Osumi & Ohira, 2009) and monitoring of outcomes (Hajcak et al., 2004). Thus, this result suggests that prior acute stress enhanced the attention and monitoring of feedback signals for learning via the stress-related cue. Additionally, the results of SEM and correlational analyses indicate that HR deceleration was independent from choice behaviors. These results imply that the PIT-like effects from the stress-related cue caused by acute stress on stochastic learning emerged via top-down descriptive processes rather than trial-by-trial, bottom-up experiential processes. Taken together, the findings in this study (Study 3) were consistent with those in Study 2 for the following points.

1. The PIT-like effects from the stress-related cue caused by acute stress happened through goal-directed processing rather than habit processing.

2. The PIT-like effects were biologically regulated by responses of the glucocorticoid system.

3. The PIT-like effects emerged though descriptive processes rather than experiential processes.

These consistencies with previous studies further certify the plausibility of the

prolonged effects of acute stress on aspects of decision-making.

Chapter 5 Conclusions

To elucidate prolonged physiological effects on decision-making under risk, this study focused on risk taking, physiological responses and psychological processes. First in this chapter, the main findings of the three studies are summarized. Second, contributions of these results are discussed in the context of previous studies examining the relationship between acute stress and decision-making under risk. Third, a possible neural model is proposed, describing mechanisms underlying these stress effects based on temporal physiological reactivity elicited by exposure to acute stress. Fourth, some limitations and suggestions for future studies are offered. Finally, conclusions regarding the present study are presented.

5.1 Summaries of findings in the present study

In Chapter 2, Study 1 preliminarily investigated whether the serotonin (5-hydroxytryptamine) transporter (5HTT) gene-linked polymorphic region (5HTTLPR) genotype affected cortisol-secretion reactivity to an acute stressor and whether reactivity returned to baseline within 90 min. For this purpose, I used the TSST, a standardized, psychological acute stress task. Study 1 examined how 5HTTLPR, one major genetic factor determining inter-individual differences in stress reactivity, could modulate, in acute stress, temporal responses of the HPA system and the SAM system. Participants carrying double copies of S alleles, indicating a high physiological responder under acute stress, and participants carrying S and L alleles, indicating low physiological responders, completed the TSST. Endocrine parameters and HR were measured and compared before, during, and after the task. This result confirmed greater transient increases in glucocorticoid and HR response after the stress task in SS allele participants than it did in SL allele participants. Additionally, transient increases induced by acute stress return to baseline later regardless of 5HTTLPR genotypes.

In Chapter 3, Study 2 investigated prolonged effects of physiological responses

induced by acute stress on risk taking in decision-making. The TSST was administered as an acute stressor; thereafter, a decision-making task was performed in which participants needed to choose a sure option or a gamble option in gain and loss frame trials 2 hours after (non)exposure to the stressor. Increased cortisol, adrenaline, HR, and subjective stress levels validated the manipulation of acute stress. Stressed participants made fewer risky choices only in the gain domain, but no effect of stress was shown in the loss domain. Deceleration of HR, reflecting attention, was greater for gains compared with losses only in the Stress group. Risk avoidance was determined by increased levels of cortisol caused by acute stress. These results suggested that acute stress modulated prolonged effects on the evaluation of risks and the monitoring of outcomes in decision-making.

In Chapter 4, Study 3 additionally investigated whether inner states of participants, affected by prior acute stress responses, specifically enhanced or reduced motivation for monetary reward in the decision-making task under risk (in Study 2). For this purpose, the study used a Pavlovian-instrumental transfer (PIT)-like experimental paradigm, in which a stress-related cue was presented in the decision-making task in Study 2. Then in Study 3, its influences on a stochastic learning task were examined. Results showed that prior acute stress enhanced effects of stress on amplifying the rate of choice of an advantageous option, selectively, in the Congruent group, associated between the stress-related cue and the advantageous choice. This result suggested that the enhancement of preference for a cautious option (Study 2) was caused by promoting motivation to obtain a reward. The second purpose of this study was to examine whether predicted effects of the stress-related cue were mediated by goal-directed processing or by habitual processing. I demonstrated that participants' decision-making was influenced by the stress-related cue only when their choices could alter probabilities of obtaining the reward (the Contingent condition) and *not* when their decision-making could *not* affect probabilities of obtaining the reward (the Random condition). This result suggested that effects of the stress related cue were mediated by goal-directed processing rather than habit processing. Furthermore, results of multiple-group structural equation modeling (SEM) suggested, even though statistical

requirements were not adequately satisfied, that the association between cortisol reactivity and the magnitude of the PIT-like effects might later be mediated mainly by responses in the glucocorticoid system.

5.2 Primary contributions of the present study to the prolonged effects of acute stress on decision-making

5.2.1 Empirical findings on the prolonged effects of acute stress on decision-making

This section discusses empirical results of present studies in the context of previous studies concerning prolonged effects of acute stress on decision-making, including risk. The main finding here is that prolonged effects of acute stress enhanced the preference for caution options only for the gain domain in decision-making under risk. No study had previously examined prolonged effects of acute stress on risk-taking in decision-making. Furthermore, the present thesis showed that prolonged effects were determined by physiological response due to acute stress. As clarified in Study 1, physiological reactivity concentrations of cortisol and adrenaline were mediated by the 5HTTLPR genotype. In Study 3, different patterns of the relationship between physiological responses to acute stress (only cortisol response, not adrenaline) and the rate of chosen caution options were observed. Results suggest that, possibly, the inner state plays an important role in decision-making after acute stress.

Study 3 revealed that prolonged effects of acute stress influenced goal-directed processing in decision-making. A previous study demonstrated that prolonged effects by glucocorticoid response promoted goal-directed decision-making (Schwabe, Vacca, Dück & Gillissen, 2009). This result might explain results of the second experiment, which suggested that preference of option, including sure reward, was specifically caused by goal-directed processing in decision-making. Possibly, indeed, stressed participants judged it better to accumulate a small and sure reward compared with pursuing the maximized, large, risky reward.

Furthermore, Study 3 illustrated that prolonged effects of acute stress promoted motivation to obtain a sure reward for results in Study 2. In research on decision-making, increased monetary motivation promotes the risky-option preference because excessive motivation focuses on the amount of reward, regardless of how low the probability of obtaining it is. However, in Study 2, prolonged effects of acute stress promoted the sure option in decision-making. Not examined in the neuroimaging study, a recent study on human relative to prolonged effects enhanced PFC activity through the activation of LTP (Henckens et al., 2011). Based on Study 3, possibly, the preference for caution options in Study 2 was caused by the promotion of the PFC, which enhanced working memory and executive function. Taken together, these empirical data consistently supported the main findings that prolonged effects of acute stress promoted the safe choice in decision-making under risk.

5.2.2 Psychological processes underlying the prolonged effects of acute stress on decision-making

5.2.2.1 Goal-directed processing vs. habitual processing

Results in Study 2 indicated a preference for cautious options for gains 2 hours after exposure to acute stress. In addition, stress-driven enhancement of a preference for gains was found only in a condition in which the EV of the sure option and that of the gamble option were identical. A conflict of choice was the maximum, whereas in conditions in which the EV of either option was greater, participants consistently made rational decisions based on the EV (Yamakawa et al., 2016). Additionally, Study 3 demonstrated that the stress-related cue influenced participants' decision-making only when their choices could alter probabilities of obtaining the reward (Contingent condition) and not when their decision-making could not affect such probabilities (Random condition).

These results indicated that prolonged effects of acute stress were mediated by goal-directed processing rather than by habitual processing. A previous study comparing the slow to the rapid effects of glucocorticoid response demonstrated

that prolonged effects of acute stress, using a laboratory task, enhanced the acceptance of unpleasant offers to maximize rewards (Vinkers et al., 2014). Present results are consistent with this finding. As most previous findings revealed that acute stress immediately prompted habitual behavior (Braun & Hauber, 2013; Schwabe et al., 2010; Schwabe & Wold, 2011), learning processing shifted from inflexible to flexible actions. Interestingly, the present study significantly observed the more cautious preference in individuals exposed to acute stress compared with those who were not exposed. In contrast, Vinkers et al. (2014) did not observe a significant difference in the rate of acceptance between the late-stress condition and the in-control condition. However, individuals in the late-stress condition tended to increase their acceptance compared with the in-control condition. Therefore, it is possible that prolonged effects promoted more flexible actions via goal-directed processing compared to the normal condition. From prolonged effects of acute stress, this thesis indicated the cautious preference in decision-making under risk. Thus, it is possible that this cautious preference was enhanced by the promotion of goal-directed processing, which caused flexible updating for information about the relationship between actions and outcomes. This result might be explained by previous findings that prolonged effects of acute stress might enhance prefrontal cortical functioning, which plays a critical role in improving decision-making to obtain a reward (Joëls et al., 2012). The influence of food-related cues on goal-directed behavior to obtain food was especially evident in situations in which participants were hungry (Perks & Clifton, 1997), suggesting the significance of such effects for adaptation. Results in this study enabled us to infer that acute stress can promote adaptive behaviors through the enhancement of goal-directed processing.

5.2.2.2 Decision by experience vs. description

The second issue is whether effects of acute stress on risk taking occur through experiential or descriptive processes (Hertwig & Erev, 2009). Results of Study 2 indicated that HR deceleration following feedback did not directly affect decision-making. In addition, HR deceleration after feedback was sensitive only to domains

(Gain vs. Loss) in Study 2 and Congruency (Congruent vs. Incongruent) in Study 3, but not to outcomes (Hit vs. Miss) in Studies 2 and 3. Independent between-HR deceleration and decisions and undifferentiated HR deceleration to Hit and Miss outcomes did not support the experience account, which is learning processes according to the online evaluation of positive and negative outcomes of stress effects on decision-making. According to the results of Studies 2 and 3, prolonged effects of acute stress influenced decision-making under risk through descriptive processes. In studies immediately after acute stress, two previous findings observed that rapid effects influenced risky choices in decision-making via the descriptive account but not the experiential account (Buckert et al., 2014; Wegier & Spaniol, 2015). From results in the present thesis, acute stress affected decision-making through descriptive processes regardless of the elapsed time after acute-stress exposure.

For rapid effects, there were some possibilities that acute stress prompted risky choices in decision-making via the descriptive account (Buckert et al., 2014) and that acute stress prompted risk seeking only for gain and inhibited risk taking only for losses (Wegier & Spaniol, 2015), but no consideration for prolonged effects was reported. As described above, contrarily, prolonged effects enhanced the cautious preference for the gain domain only in decision-making via the descriptive account. Possibly, this contradictory result was caused by differences of activity in the PFC. This description process is based on evaluations of the magnitude of reward and probability. As prolonged effects activate the function of PFC, individuals might be using these resources effectively in decision-making a few hours after acute stress. Altogether, present results were more consistent with the descriptive account, indicating that acute stress can affect the cautious preference in decision-making through a top-down altering of representations for structures of decision-making.

5.2.2.3 Enhancement of motivation to obtain rewards vs. reduction of attraction of rewards

The third important account is the motivational strength to obtain a reward in decision-making under risk. In Study 3, prior acute stress enhanced effects of the

stress-related cue, amplifying the rate of choosing an advantageous option, but it was selective in the Congruent group in which the stress-related cue was associated with the advantageous option. Additionally, this resulted from the stress-related cue enhancing the reinforcement learning rate in the Congruent group. Thus, the enhancement of preference for a cautious option in Study 2 was caused by the promotion of motivation to obtain a reward. For rapid effects of acute stress on decision-making, most previous findings have consistently suggested that acute stress immediately increased motivation to obtain a reward, resulting in the enhancement of reinforcement learning (Lighthall et al., 2011; van den Bos, et al., 2009). These studies indicated that excessive motivation to obtain a reward prompted a preference for risky choice compared with sure choice because excessive motivation focused on the amount of reward regardless of the low probability of obtaining it. However, the present result showed that excessive motivation to obtain a reward related to the preference for sure choice. This inconsistent result between rapid and slow effect might be explained by the reinforced learning rate as an index of modulation in reward prediction error, defined by the discrepancy between the reward and its prediction (Schultz, Dayan & Montague, 1997) in each trial. In the present study, prolonged effects related to the promotion of learning rate. In fact, prolonged effects might enhance the modulation of information and motivation to obtain a sure reward from decision-making, resulting in a preference for cautious options.

5.2.3 Possible time-dependent model describing mechanisms underlying effects of stress on decision-making

5.2.3.1 Biological time-dependent response mechanisms induced by acute stress in previous study

A previous study suggested that prolonged effects of acute stress are activated by a biological time-dependent response induced by acute stress. Several hours after exposure to an acute stressor, genomic processes begin, resulting in modulation of neurotransmission (Diamond, Campbell, Park, Halonen, & Zoladz,

2007) (Figure 5.1). Specifically, cortisol—mainly glucocorticoids in humans—secreted by the HPA system on exposure to acute stress can bind mineralocorticoid and glucocorticoid receptors expressed abundantly in the brain (de Kloet, Joëls, Oitzl, & Sutanto, 1991). During several hours after onset of acute stress, glucocorticoid can be mediated via these receptors and thus continue to influence neural plasticity for several hours (Joëls, Wiegert, Oitzl, & Krugers, 2006). Based on animal studies of underlying mechanisms, some human studies have revealed that long-term potentiation (LTP) of neurons was attenuated in the amygdala and hippocampus (Henckens, van Wingen, Joëls, & Fernández, 2010), whereas LTP in the prefrontal cortex (PFC) related to cognitive control was restored to baseline or

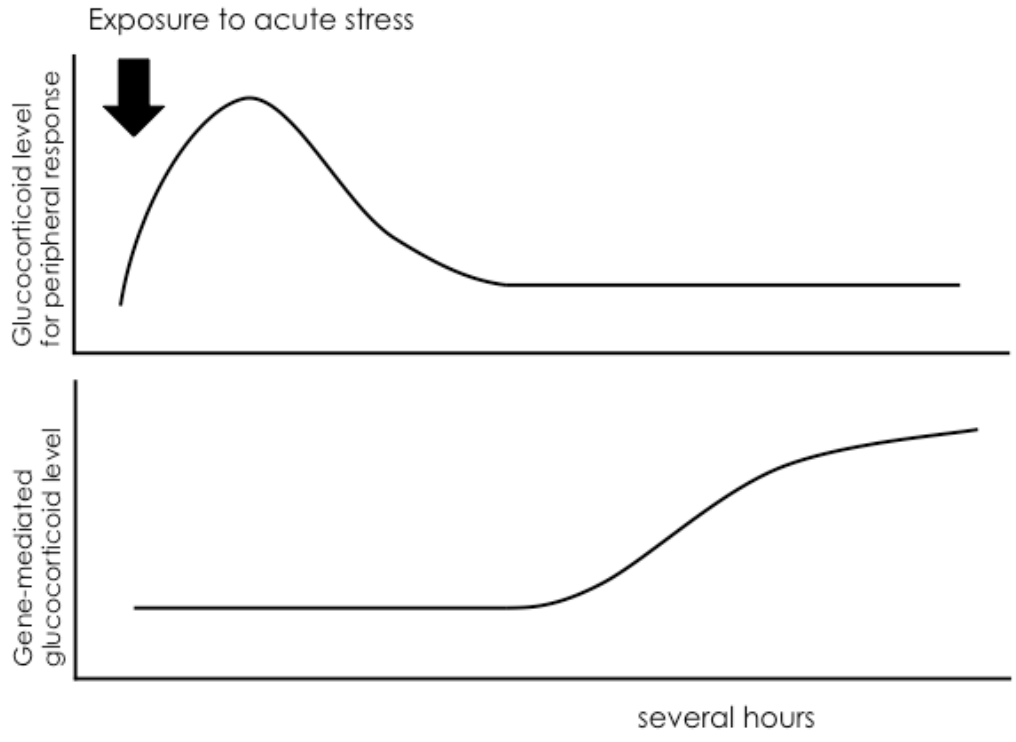


Figure 5.1. Prolonged response of glucocorticoid system under acute stress.

further facilitated compared with baseline (Henckens, van Wingen, Joëls, & Fernández, 2011). This prolonged effect of acute stress via the glucocorticoid system restores homeostasis by diverting energy supply to challenged tissues and controls the excitability of neuronal networks (de Kloet et al., 1991).

As described above, physiological responses temporally mediate the central nervous system related to cognitive and emotional processes underlying decision-making. Possibly, this time-dependent effect causes complicated and mixed findings for effects of acute stress on decision-making.

5.2.3.2 Possible neural function model describing mechanisms underlying effects of stress on decision-making based on temporal physiological responses

Based on these previous results and current findings, I propose a new possible time-dependent model describing prolonged effects of acute stress on decision-making under risk (Figure 5.2.). This model shows how time-dependent effects of acute stress influence activity in the three regions in the brain, which play important roles in decision-making under risk.

	Immediately	Later
Prefrontal cortex	−	+
Amygdala	+	+／−
Striatum	+	+

Figure 5.2. Hypothetical time-dependent model.

One of these key regions is the PFC, which is believed to play an essential role in cognitive control. In reviews, rapid effects of acute stress regulate the induction of LTP in the PFC (Arnsten, 1998; Diamond et al., 2007) via functional alteration in glucocorticoid receptors. Empirical evidence has demonstrated that patients with PFC dysfunctions indicate impairments in decision-making under risk (Brand et al., 2005; Manes et al., 2002; Starcke & Brand, 2012). Namely, PFC suppression causes a reduced ability to perform well in complex tasks like adaptive decisions that include risk. In contrast, Henckens et al. (2011) observed PFC promotion a few hours after acute stress, accompanied by the enhancement of working memory. The present studies, especially Studies 2 and 3, demonstrated the possibility that prolonged effects of acute stress enhanced the preference for cautious options for the gain domain and the promotion of goal-directed processing. Goal-directed processing is regulated by the activation of the PFC (Balleine & Dickinson, 1998; Miller & Cohen, 2001). Therefore, cautious decisions under risk via prolonged effects of glucocorticoid response result from updating information through goal-directed processing, caused by LTP activation in the PFC. Moreover, this study revealed that prolonged effects of acute stress influenced risk taking through the descriptive account. Because the descriptive account related to the evaluation of the magnitude of reward and probability, cautious decisions due to prolonged effects were caused by top-down regulation rather than bottom-up regulation. As PFC activation is known to prompt top-down regulation, prolonged effects of acute stress enhanced top-down regulation by the activation of the PFC, causing the promotion of the descriptive account.

Second, this thesis focused on the activation of the amygdala, a key modulator of vigilance and emotional processing (Phelps & LeDoux, 2005; van Marle et al., 2009). Administration of a cortisol tablet immediately diminished the activity of the amygdala to happy and fearful faces, but activation to fearful faces returned to normal levels 285 min later, whereas activation to happy faces was still dampened after 285 min (Henckens et al., 2010). The time-dependent characteristics of the amygdala involved in the reflection effect might lead to a negativity bias in processing emotional information. This cerebral activity by gene-mediated effects

might lead participants to avoid the gamble option in the gain domain 2 hours after exposure to acute stress. In addition, inhibitory activation of the amygdala by slow effects of acute stress related to the PFC (Henckens et al., 2010). The activity of the amygdala was suppressed by the PFC during the regulation of emotional responses (Beauregard et al., 2001; Kompus et al., 2009). A preference for cautious options in the gain domain might be regulated by the inhibitory activity of the amygdala, controlled by the enhancement of the PFC.

The third issue is the striatum, which plays necessary roles for the dopaminergic system in reward anticipation. Acute stress immediately leads to increased dopaminergic signaling in the striatum, mediated by glucocorticoid (Adler et al., 2000; Piazza & LeMoal, 1997; Pruessner, Champagne, Meaney &Dagher, 2004; Scott, Heitzeg, Koeppe, Stohler & Zubieta, 2006). In contrast, slow effects of glucocorticoid response under acute stress have never been found. Although the current studies did not deal with neural data, given the empirical findings in Study 3 and in section 5.2.2.3, it was assumed that prolonged effects enhancing motivation to obtain a reward were caused by striatum activation 2 hours after acute stress.

In sum, the cautious preference for gain domain, as observed in the present studies, might be caused by inhibited impulsivity to a large monetary reward because of the reductive amygdala, mediated by the activation of the PFC. Furthermore, the cautious preference might be caused by goal-directed processing and top-down regulation due to the enhancement of the PFC. Additionally, enhanced motivation to obtain a sure reward depended on the activation of the striatum.

5.2.4 Limitations of the present study

Limitations of the present research should be noted. First, the samples are relatively small sizes. As reported in the results section, the effect sizes (η_p^2) of most significant effects were within a reasonable range. Thus, the results reported in this study can be considered mostly acceptable. However, before drawing any

concrete conclusions, present findings should be replicated with a larger sample. Furthermore, the sample in present studies consisted of only male participants, in order to avoid endocrine variations caused by women's menstrual cycles. Because previous studies (Preston et al., 2007; van den Bos et al., 2009) reported gender differences in stress effects on risk taking, the generalizability of present findings must be delayed until after studies with samples that include both sexes.

Second, interpretations of the current findings remain speculative because I did not perform a neuroimaging study. Neuroimaging studies for the prolonged effects of acute stress remain rare. Mechanisms underlying the current findings should be explored using neuroimaging and/or pharmacological manipulations.

Finally, other possible physiological pathways mediating effects of acute stress on decision-making should be examined. For example, peripheral pro-inflammatory cytokines, such as interleukin (IL)-1β and IL-6, increase within 2 hours after acute stress (Brydon et al., 2010; Yamakawa et al., 2009). These cytokines reach the brain via leaky regions of the blood–brain barrier and afferent nerve fibers (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008; Raison, Capuron, & Miller, 2006), and they can affect activity in such brain regions as the amygdala and anterior insula, both related to affective response (Harrison et al., 2009) and leading to the modulation of social decision-making (Ohira, Osumi, Matsunaga, & Yamakawa, 2013).

To my knowledge, despite these limitations, the present study first evidenced that acute stress has prolonged influences for hours after exposure to a stressor, leading to a cautious shift in decision-making for gains. The present findings provided significant implications for the involvement of physiological and somatic factors in decision-making (Ohira, 2010; Ohira et al., 2010, 2013, 2014).

5.2.5 Conclusions

The present thesis aimed to refine information on prolonged effects of acute stress on decision-making under risk, via physical responses elicited by exposure to acute stress. Present results revealed that acute stress promotes a cautious preference only for the gain domain in decision-making under risk 2 hours after

stress onset. As observed later, this cautious preference might be caused by inhibited impulsivity to a large monetary reward because of the reductive amygdala mediated by PFC activation. Furthermore, the cautious preference might be caused by goal-directed processing and top-down regulation due to PFC enhancement, and, additionally, enhanced motivation to obtain a sure reward depended on the activation of the striatum.

Influence of acute stress on behavior functions significantly toward adaptations in changing environments. I wonder what meaning rapid and prolonged effects of acute stress, respectively, have on decision-making for adaptation. From previous findings, the rapid effects of acute stress reduce the ability to evaluate situations, with the organism being affected by emotional information immediately after the onset of acute stress and thus causing emotional decisions that lack careful consideration. In contrast, prolonged effects prompt the cautious preference using resources (outcome and option) effectively. Namely, prolonged effects aim to regain the calm lost by exposure to acute stress. In their review, de Kloet, Karst & Joëls (2008) explained that delayed response to acute stress in the brain might help normalize excitability evoked by rapid, non-genomic effects. Findings in the present thesis assumed that the potential role of prolonged effects under acute stress helped an organism return a lost calm to its normal state.

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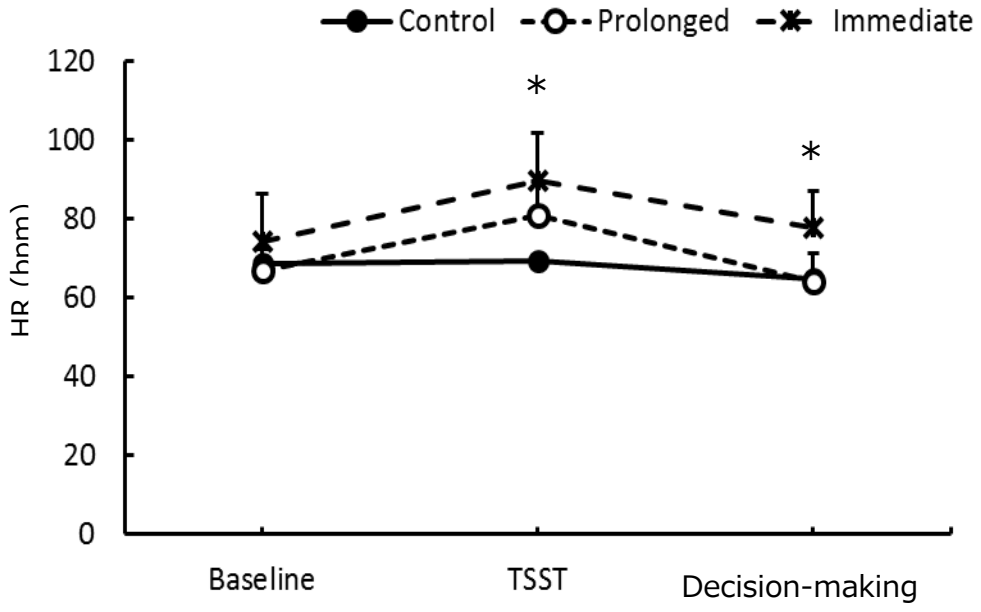
Supplement

Effects of acute stress on decision-making immediately after exposure to a stressor were examined. Nine Japanese male undergraduates at Tokaigakuen University (age range 20-29) participated in the experiment. After the first rest period of 10 minutes, the first saliva sample was taken as a Baseline. Next, participants performed the Trier Social Stress Test (TSST) (Kirschbaum et al., 1993) as an acute stressor. Finally, the participants conducted a decision-making task, which was identical with the task used in Experiment 2. The third and fourth saliva samples were taken at every 2 blocks of the decision-making task (DM 1, DM2). To examine the immediate effects of stress, heart rate (HR), rates of gamble choice, HR deceleration in the Immediate group were compared with those indices in the Control group and the Stress group in Experiment 2 (the "Stress group" is renamed as the "Prolonged group" in this supplement). In this additional experiment, cortisol levels were determined from saliva samples. Thus, the cortisol level in the Immediate group could not be compared with cortisol levels in other groups which were determined from blood samples.

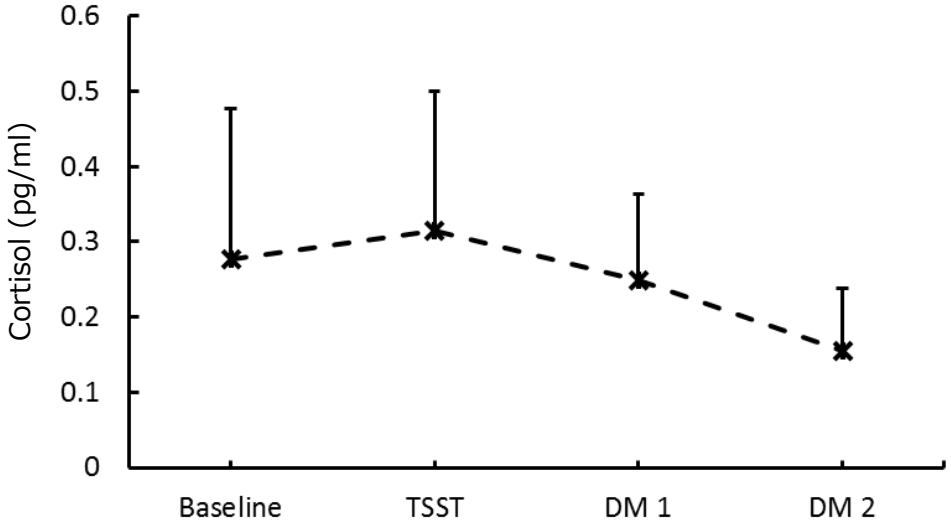
Results of HR and cortisol data are presented in Supplemental Figure S1 and S2. For HR, a significant interaction between Group (Prolonged, Control, and Immediate) and Period (Baseline, TSST, and Decision-making) was found ($F(4, 64) = 13.62$, $p < .05$, $\eta_p^2 = 0.46$). The increase of HR in the Immediate group was greater during Task and DM periods compared with the Control group ($p < .05$). For cortisol concentrations, there was a significant effect of Period ($F(3, 21) = 4.09$, $p < .05$, $\eta_p^2 = 0.37$), but no difference was observed during Task and DM periods compared with Baseline ($p < .05$). The rates of gamble choice are shown in Supplemental Figure S3. There was a significant interaction between Group (Prolonged, Control, and Immediate), Domain (Gain vs. Loss), and EV level (Large, Equal, and Small) ($F(4, 64) = 3.21$, $p < .05$, $\eta_p^2 = 0.17$). Further analyses ($p < 0.05$) indicated that the rate of gamble choice in the High EV level for the Gain domain in the Immediate group was smaller than those in the Control and Prolonged groups. As shown in Supplemental Figure S4, the variation of HR time locked to presentation of outcomes of gamble showed deceleration that can be interpreted as a typical orienting response. Two participants were excluded from the analysis of HR because of technical problems in data collection. A three-way interactions of Group (Stress, Control, and Immediate), Domain (Gain vs. Loss), and Outcome (Hit vs. Miss) for the HR deceleration did not reach to significance ($F(2, 30) = 0.13$, *n.s.*, η_p^2

= 0.009).

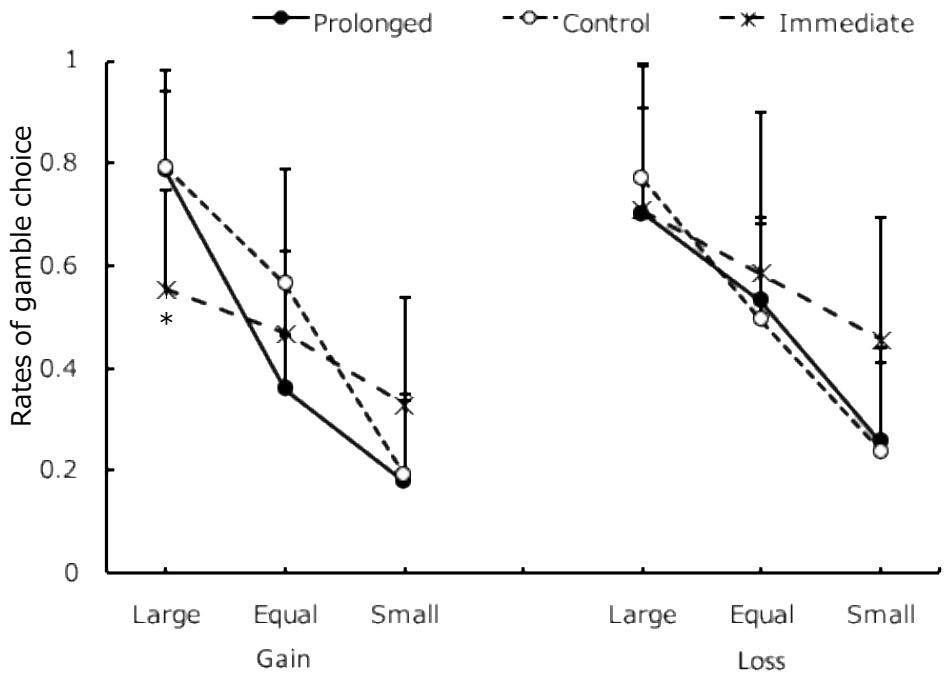
Acute stress, immediately after exposure to the stressor, made the participants insensitive to EV of options, especially in the gain domain. At earlier stages of acute stress, functions of the prefrontal cortex (PFC) are down-regulated, via functional alterations in glucocorticoid receptors (Arnsten, 1998; Diamond et al., 2007). Thus, insensitivity to EV in decision-making in the Immediate group should be attributed to impairments of exact evaluations of EV of options caused by reduced functions of the PFC. Taken together, acute stress showed temporally differentiated effects on decision-making.



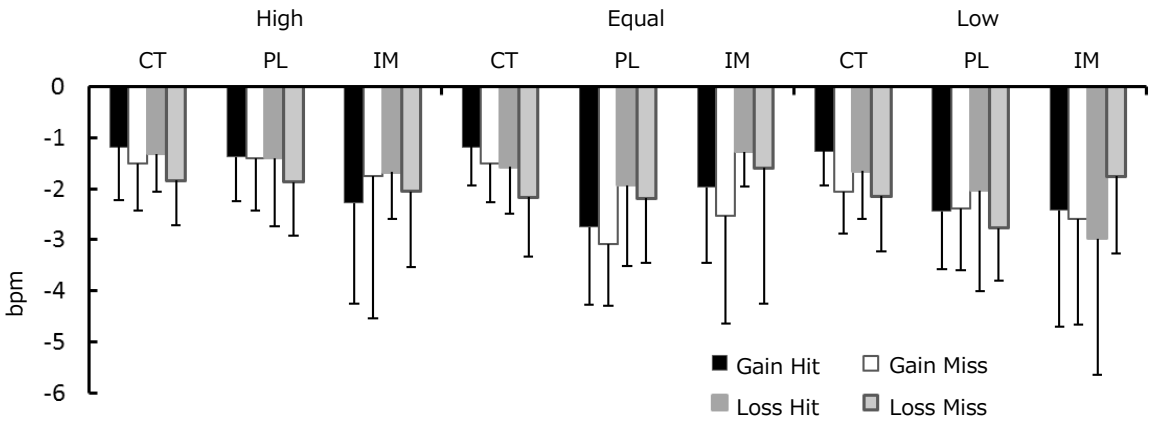
Supplement Figure S1. HR in each group.



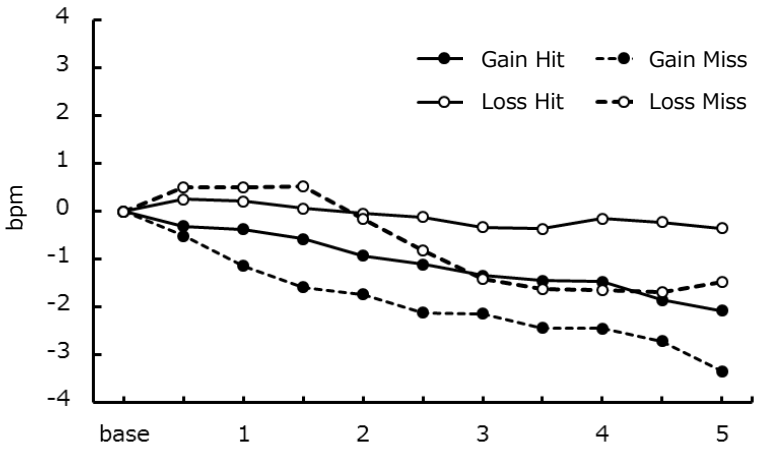
Supplement Figure S2. Cortisol levels in Immediate group.



Supplemental Figure S3. Rates of gamble choice.



a. HR deceleration



b. HR response on Immediate group

Supplemental Figure S4. (a) HR deceleration in decision making task. (CT = Control group, PL = Prolonged group, IM = Immediate group) (b) Waveforms of time series variations of HR.