ABSTRACT

Title of Dissertation: Interactions between appetitive and aversive processing in the human brain

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The brain mechanisms underlying anxiety/stress and motivation have been investigated extensively. However, they were mainly investigated independently of each other. Even though some studies discussed interactions between these two mechanisms, our understanding of the interaction between anxiety/stress and motivation is still limited. Motivation can be divided into two aspects. One is appetitive motivation to win appetitive outcome, and the other is aversive motivation for avoiding aversive outcome. Accordingly, in current functional MRI study, it was investigated how appetitive/aversive motivational processing would be influenced by anxiety/stress. In the first experiment I investigated interactions between threat and reward processing during anticipation of electric shock and monetary reward. Analysis of skin conductance data during a delay phase revealed competitive interaction between threat and reward processing. Analysis of imaging data during a delay phase also revealed the interaction effect in several regions, including midbrain/ventral tegmental area, caudate, putamen, bed

nucleus of the stria terminalis, anterior insula, middle frontal gyrus, and dorsal anterior cingulate cortex. In the second experiment, the interaction between threat and reward/punishment processing was investigated. Analysis of imaging data during a delay phase revealed competitive interaction between threat and reward processing in left caudate. However, responses in the same site did show interaction between threat and punishment processing. Taken together, the findings in two studies suggest competitive processes of threat and reward, and independent processes of threat and punishment.

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INTERACTIONS BETWEEN APPETITIVE AND AVERSIVE PROCESSING

IN THE HUMAN BRAIN

by

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CHAPTER 1: Background

In daily life, we are exposed to an overwhelming amount of information, but only have limited capacity to process the information. In order to guide behavior efficiently, the brain has to select stimuli which are "worthy" to be further processed. The selective mechanism enables an organism to achieve current goal, and ultimately to survive. Traditionally, two types of attentional control in selection mechanisms have been suggested. One is stimulus-driven (bottom-up) and the other is goal-directed (top-down; Corbetta&Shulman, 2002, for review). For instance in visual processing, a salient stimulus (e.g. yellow circle scattered with gray ones) would capture visual attention (bottom-up processing; e.g. Theeuwes, 1992), or visual attention can be assigned to task-relevant stimulus (top-down processing; e.g. Francolini & Egeth, 1979).

The selective mechanism can also be applied to emotional processing. For instance, Öhman (2002) suggested that affectively significant stimulus can be prioritized in the information processing. Emotional salient stimulus (e.g. snake) captures attention, resulting in faster detection than emotion-neutral stimulus. In line with his account, dual-competition model was proposed to explain interaction between emotion and cognition (Pessoa, 2009). According to the model, processing of emotional stimuli demand attentional/effortful resources which are required for other executive functions. The resources are limited in capacity, thus if attentional resources are utilized in processing of task-irrelevant emotional stimulus, cognitive processing for task performance is impaired.

The competition of attentional/effortful resources is not limited to processes driven by physical stimuli. Recent studies have attempted to understand the impact of emotion on cognition in extended manner, such as mental states. According to Salzman and Fuzi (2010), a mental state is integration of feelings, intentions, memories, characteristics, etc., which adjusts

behaviors at the moment. Thus, an organism's behavior depends on mental state, which can be divided as a function of valence – positive or negative.

1.1. Negative mental state: anxiety/stress

Anxiety can be defined as the mental state which is elicited by temporally, physically, and psychologically distal threat. Thus, it is a mental state activated by unpredictable threat, contrasting to fear which is responses to imminent danger (Davis et al. 2010, for review). In anxious or stressful circumstances, even though threat or danger is not imminent, adaptive responses would be required to be ready to take action against the unpredictable threat such as being vigilant or cautious (Robinson et al, 2013). According to recent proposals, the impact of anxiety or stress influences cognitive system by modulating attentional system (Derryberry and Reed, 2002; Eysenck et al., 2007; Pessoa, 2009).

1.1.1. Cognitive processing in anxiety/stress

It has been suggested that emotion-laden stimuli are prioritized in perceptual processing. For instance, threatening stimuli are detected faster in emotionally neutral ones (Öhman et al., 2002). It was proposed that salient stimuli that are especially important for survival are prioritized in processing. This framework can be extended to circumstances in which the impact of the negative stimulus is temporally extended. For instance, Phelps et al. (2006) showed that presentation of fearful face enhanced perceptual sensitivity to subsequent visual stimulus. In similar circumstances, even when the negative stimulus does not exist but negative mental state

(e.g. sadness) is induced the subsequent visual processing is influence by the negativity (Gasper & Clore, 2002).

Recently, converging evidence indicates that anxiety or stress changes the information processing in the early stage by heightening vigilance or sensitizing stimulus features. For instance, Shackman et al (2011a) investigated neural activities while participants were performing visual discrimination task under threat of shock. When electric shock was anticipated, an early sensory-specific ERP components generated in extrastriate cortex (N1) were higher than safe. In another study about auditory processing, Cornwell et al. (2007) reported that the neural responses to an auditory oddball, measured by MEG, were heightened during threat block. Moreover, source localization analysis implied that activity in brain structures related to threat processing, such as amygdala and insula, was increased under threat. Similar results were also reported by Baas et al. (2006) in ERP component (wave V).

The impact of threat-related processing on cognition also can be found in executive function, including cognitive control (Blair et al., 2007; Choi et al, 2012; Hart et al., 2010; Kanske and Kotz, 2010) and working memory (Anticevic et al., 2010; Dolcos and McCarthy, 2006). It has been suggested that anxiety or stress would impair the cognitive processing by dispersing attentional resources (Derryberry and Reed, 2002; Eysenck et al., 2007). Similarly, dual-competition model (Pessoa, 2009) suggests that anxiety or stress exploits attentional resources which are also necessary for executive function, resulting in the impairment of the performance. For instance, the Stroop task is often considered to require attentional control during the task performance (Roelofs, 2003 for review). Using a variant of Stroop task, Choi et al. (2012) showed that the conflict processing was compromised under threat of shock. In their study, a picture was presented as a target along with a distracting word. The distracting word could be either

matched to target picture (congruent condition), unmatched (incongruent condition), or string of Xs (neutral condition). Prior to the target display presentation, a cue was presented informing a chance of electric shock. The behavioral result revealed that the interference effect (incongruent vs. neutral) was increased under threat of shock than safe condition.

Taken together, the findings indicate that anxiety/stress would enhance bottom-up attentional control to makes an organism vigilant to environment, resulting in enhancement of perceptual processing. However, the top-down attentional control would be impaired under anxiety/stress. In Stroop-like task (e.g. Choi et al., 2012) in which two types of stimulus is presented simultaneously (e.g. task-relevant and task-irrelevant), thus top-down control is required to select relevant stimulus or resolve the conflict between target and distractor. If the processing requires processing resources because of interference or maintaining working memory, anxiety/stress impairs the attentional control.

1.1.2. Neural mechanism of anxiety/stress

Previous studies have identified the amygdala as a key region in fear processing (LeDoux, 2000, for review). A number of animal and human imaging studies observed greater neural responses in amygdala to CS+ stimulus (paired with electric shock) comparing to CS- stimulus (Büchel et al., 1998; LaBar et al., 1998; Lim et al., 2009).

However, unlike imminent fear, anxious states or sustained fear elicit neural responses in the bed nucleus of the stria terminalis (BNST). A body of animal studies with lesions or pharmacological manipulations indicates that distal threat or context fear engages BNST processing (Walker and Davis, 1997; Sullivan et al., 2004). Imaging studies also reported that

BNST is involved in the processing of distal or unpredictable threat, such as anxiety state (Kalin et al., 2005; Mobbs et al., 2010; Somerville et al., 2010; Davis et al., 2010 for a review). Some of these studies also reported recruitment of anterior insula and dorsal anterior cingulate cortex (ACC) during threat processing. The anterior insula is a hub region in salience processing (Menon&Uddin, 2010). Additionally, it is involved in the processing visceral sensory information and mapping the internal state of the body (Craig, 2002, 2009). Imaging studies with human (Banks et al., 2007; Mobbs et al., 2010) and non-human primates (Kalin et al., 2005) revealed that the medial PFC is involved in regulatory function of threat (Ochsner & Gross, 2005, for review).

1.2. Positive mental state: motivation

When negative outcome is anticipated but uncertain, an organism would assess the risk of threat, and/or withhold action (McNaughton & Corr, 2004). On the contrary, if a rewarding outcome is expected, behaviors towards the reward will be motivated. To investigate reward processing, the monetary incentive delay (MID; Knutson et al, 2000) task is commonly used in human cognitive experiments. In the MID task, typically, reward processing is manipulated by presenting a visual cue (e.g. dollar symbol). After a short delay period, a target display is presented. If participants respond fast and accurately, they receive a bonus monetary reward.

1.2.1. Cognitive processing in motivation

In general, anticipation of monetary reward enhances task performance. For instance, simple target detection was faster and accurate in reward trials than no-reward trials (Carter et al.,

2009; Hardin et al., 2006; Zink et al. 2004). However, the shorter RT in reward trials might be due to general arousal effect by reward anticipation. In addition, experimental manipulation for reward condition would naturally enforce faster responses because participants were required to respond faster than certain threshold to obtain reward.

Engelmann and Pessoa (2007, 2009) showed that motivation sharpens stimulus processing by manipulating level of motivation with multiple incentive values. In their experiments, a spatial cue was presented before target display. Participants were instructed to detect the spatial location of the target picture (left or right of screen) as quickly and accurately as possible. The behavioral results revealed that detection sensitivity (d') increased parametrically with reward value, implying that reward anticipation does not simply evoke general arousal but has specific effect on perceptual processing. In their study (Engelmann et al., 2009), functional imaging data revealed correlations of neural responses to the rewarding value in visual cortex, reward circuitry, and fronto-parietal attentional regions. In parallel, Rowe et al. (2008) showed that reward anticipation increased sensitivity to reward-relevant modality of stimulus while the sensitivity to reward-irrelevant stimulus modality was decreased. In addition, the modality specific effect of reward was observed in fronto-parietal network. These findings indicate that appetitive motivation enhances perceptual processing via adjusting attentional control.

The impact of reward anticipation on cognition also can be found in executive function, including cognitive control (Padmala et al., 2011), spatial working memory (Kennerley & Wallis, 2009), and response inhibition (Padmala & Pessoa, 2010). For instance Padmala et al. (2011) used a variant of Stroop task in which a picture was presented as a target stimulus along with a word as a distractor which could be either matched to target picture (congruent condition) or

unmatched (incongruent condition), or string of Xs (neutral condition). Prior to the target display presentation, a cue was presented informing motivational condition (reward or non-reward). The behavioral result revealed that the interference effect (incongruent vs. neutral) was decreased when monetary reward was expected. Functional imaging data revealed that neural responses in fronto-parietal regions during reward anticipation.

Taken together, motivation seems to adjust bottom-up and top-down attentional control by enhancing perceptual sensitivity and allocation processing resources to win reward.

1.2.2. Neural mechanism related to positive emotional state

Midbrain dopaminergic neurons and their major target – the ventral striatum – play a key role as neural mechanisms of motivational processing. In the animal literature with physiological measurement as well as lesion and pharmacological manipulation, neurons have been found to respond during reward anticipation in the nucleus accumbens (NAc), putamen, and ventral tegmental area (Apicella et al., 1991; Bissonette et al. 2013; Phillips et al., 2003; Schultz et al., 1992; Parkinson et al., 2000; Cardinal et al., 2002; Smith & Dickinson, 1998; Taylor & Robbins, 1984; Cador et al, 1991). In human imaging studies using the MID task putative reward-related brain regions, including the NAc and dopaminergic midbrain, showed greater activation during processing of reward compared to no-reward cues (Carter et al. 2009; Knutson et al, 2001; Padmala et al., 2011).

Other brain regions engaged in reward processing are anterior insula and medial PFC. Recent studies have observed activation in this region during appetitive processing, including to cues signaling monetary gains (Liu et al., 2011; Padmala & Pessoa, 2011; Samanez-Larkin, et al.,

2007). Furthermore, anterior insula neurons increased responses when monkeys knew they would, or might receive, a reward based on performance (Mizuhiki, et al., 2012). In addition, many studies have reported dorsal ACC responses to reward, especially when the task requires adjusting behavior to win reward (Bush et al., 2002; Shidara & Richmond, 2002; Shima & Tanji, 1998).

1.3. Overview

Disposition of anxiety/stress and motivation is distinguishable not only in aspect of its valence (i.e. negativity and positivity), but also in the way of the impact on the attentional processing. According dual competition hypothesis (Pessoa 2009), the processing of emotionally salient stimuli competes with other executive functions for attentional resources. The resources are limited in capacity, thus, if attentional resources are used to process task-irrelevant emotional stimuli, concurrent or subsequent task performance is impaired. This hypothesis also can be applied to aversive/appetitive mental state. For instance when an electric shock is anticipated and unavoidable, attentional resources would be utilized in processing of the shock, resulting in impairment of task performance (e.g. Choi et al., 2012). On the contrary, if monetary incentives are expected depending on task performance, attentional control would be enhanced to maximize chance to win the reward (e.g. Padmala et al., 2011). In sum, anxiety/stress and motivation have contrasting effect on attentional control.

Motivation can be divided into two aspects. One is appetitive (or approach), and the other is aversive (or avoidance) motivation (Elliot & Covington, 2001 for review). Both types of motivation are important determinants of behavior in the aspect of energization (Elliot 2006) or motivational salience (Zink et al, 2004). However, they differ in valence. The appetitive

motivation drives an organism toward appetitive stimuli/outcomes (i.e. reward anticipation) whereas the aversive motivation directs an organism away from aversive stimuli/outcomes (i.e. punishment anticipation). Some studies reported that not only monetary gains but also losses evoked similar activation in the striatum during the outcome anticipation (Carter et al., 2009; Wu et al., 2014). Other studies, however, showed that the level of activation (Tom et al, 2007) or location of activation (Seymour et al, 2007) in the striatum is dependent on motivational valence (i.e. reward or punishment anticipation). Based on the mixed results about appetitive and aversive motivation, it is still unclear what the neural substrates of these processes are, and how they are represented in the brain.

The majority of research on appetitive and aversive processing has focused on behavioral and neural responses that occur when rewarding or punishing outcomes are delivered. However, less is known about how appetitive and aversive processes operate during the anticipation of an outcome and how they interact with each other during the anticipation. Therefore, in this dissertation, I will investigate how stress influences appetitive motivation as well as aversive motivation. Specifically, I will focus on how the threat of shock influences neural processes when monetary reward and/or punishment are anticipated.

CHAPTER 2: Interaction between threat and appetitive processing

Introduction

The brain mechanisms underlying appetitive and aversive processing have been investigated, by and large, independently of each other. Although many investigators have discussed interactions between these two systems (e.g., Koob & Le Moal, 2008; Leknes & Tracey, 2008), our knowledge about how they may act *simultaneously* in the brain is rudimentary. Recent studies that investigated interactions between appetitive and aversive processing focused on decision making (Amemori & Graybiel, 2012; Park et al., 2011; Talmi et al., 2009). Overall, the understanding of appetitive-aversive interactions during basic perceptual and attentional processing is currently lacking.

Midbrain dopaminergic regions and their projection sites in the striatum are implicated in appetitive processing (Delgado, 2007; Haber & Knutson, 2010; O'Doherty, 2004; Schultz et al., 2000). However, these regions also participate in aversive processing, indicating that they are involved in both appetitive and aversive motivation (Bromberg-Martin et al., 2010; Salamone, 1994). Conversely, from the opposite valence, processing in the amygdala, bed nucleus of the stria terminalis, and anterior insula has been frequently linked with aversive events or stimuli (Adolphs & Tranel, 2000; Craig, 2002, 2009; Davis et al., 2010; LeDoux, 2000). Yet, these regions are engaged during appetitive processing, too (Everitt et al., 2003; Liu et al., 2011; Mizuhiki et al., 2012; Salzman et al., 2007). Finally, several brain regions, including the dorsal anterior cingulate cortex (ACC) and dorso-lateral prefrontal cortex (PFC) during goal-directed behaviors, are engaged by both appetitive and aversive stimuli. Critically, in all these cases, little is known about how appetitive and aversive processing *interact*.

To investigate this question, I used both appetitive and aversive stimuli in a factorial design. Participants performed a variant of the monetary incentive delay task (Knutson et al., 2000) during which different types of visual cues informed them about the chance of winning monetary reward and/or receiving a mild aversive shock (Fig. 1). The goal of current study was to investigate appetitive-aversive interactions during the anticipation period between the cue and target phases, thus allowing me to probe stimulus-*independent* processes. How does the simultaneous possibility of reward and shock affect brain and behavior?

I tested two competing scenarios in key brain regions, including the midbrain, striatum, and anterior insula. According to the "salience hypothesis", appetitive and aversive stimuli are represented in terms of their motivational salience. For instance, a recent electrophysiological study in monkeys uncovered dopamine neurons that were excited by both reward-predicting stimuli and airpuff-predicting stimuli (Matsumoto & Hikosaka, 2009). In the present study, the salience hypothesis predicts that, in the condition involving both reward and threat, activation would be *enhanced* relative to the "single" conditions because of increased salience. According to the "competition hypothesis", reward and threat should trade-off against each other: in the condition involving both reward and threat, responses due to reward would be *reduced* during threat and responses due to threat would be *reduced* during reward. One reason a trade-off would be expected is because reward was task relevant while threat might function as a "distractor" – thus, it might lead to a competition for limited processing resources (Pessoa, 2009). Another possibility is that, in some regions, evoked responses might trade-off if positive and negative systems are organized as "push-pull", opponent systems (Konorski, 1967; Solomon & Corbit, 1974). As an example of opponency, pain reduces pleasure and reward induces analgesia (Leknes & Tracey, 2008).

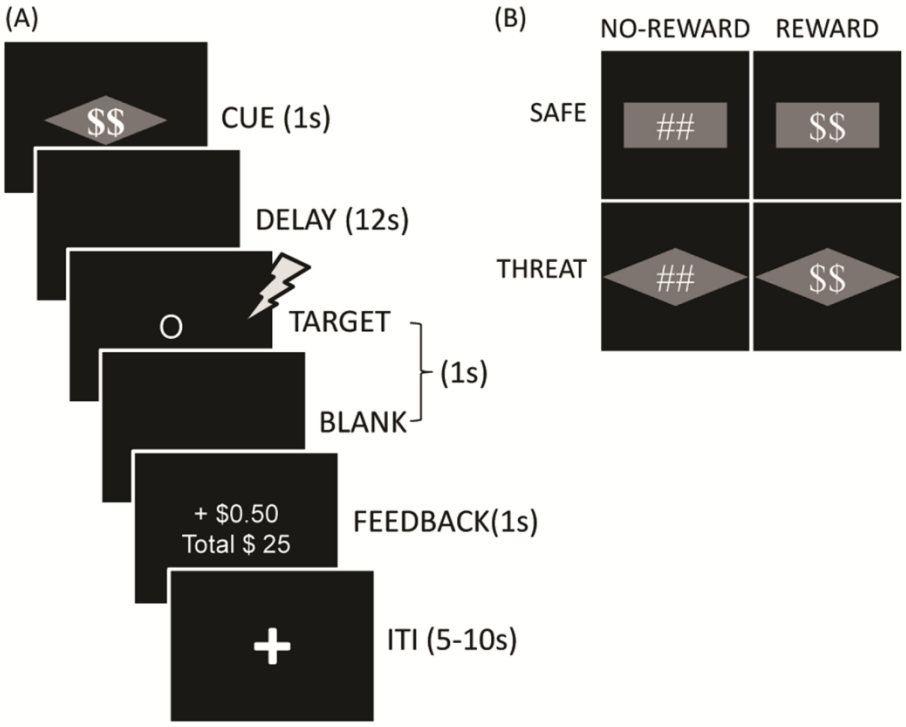

Figure 1. Task design. (A) Subjects performed a variant of Monetary Incentive Delay task. During the threat-reward condition (shown here), a visual cue stimulus (diamond-shape overlaid with dollar sign) signaled that participants could win extra monetary reward if they respond accurately before the target display disappears and also a mild electric shock could occur at the onset of the target display (independent of the performance). Participants were instructed about the meaning of the cue stimuli prior to task execution. During the target phase, participants were asked to indicate whether the shape was a circle or a square. Following the target phase, participants received feedback about the monetary reward (B) Four different types of visual cues at the start of each trial informed participants about the chance of winning extra monetary reward and/or receiving a mild aversive shock.

Materials and Methods

Subjects

Twenty-four volunteers participated in the study, which was approved by the Institutional Review Board of the University of Maryland, College Park. Based on self-report, subjects were free from psychiatric or neurological disease, or related past history. All participants were right-handed, had normal or corrected-to-normal vision, and gave informed written consent. Three

participant's data were excluded from the analysis because of head motion exceeding 3 mm. One other participant discontinued the experiment around the half-way mark and was excluded. Thus, data from twenty participants (27.92±4.61 years old; 12 females) were included in the final analysis.

Stimuli and behavioral paradigm

I employed a variant of the monetary incentive delay (MID) task (Knutson, et al., 2000). Each trial started with the presentation of a compound visual cue (1 s) that was either rectangle- or diamond-shaped, and overlaid with a pound or dollar sign (Fig. 1A). The pound/dollar sign indicated the *Reward* condition (no-reward or reward) and the geometric shape (rectangle or diamond) indicated the *Threat* condition (safe or threat). Four different types of cues were used (Fig. 1B). The dollar sign indicated the chance of winning monetary reward if the response was made correctly before the display disappeared. The geometric shape (which was counterbalanced across participants), indicated that a mild electric shock could be delivered at the onset of the target display (independent of performance). To calibrate the intensity of the electric shock, each participant was asked to choose his/her own stimulation level immediately prior to functional imaging, such that the stimulus would be "highly unpleasant but not painful". After each run, participants were asked about the unpleasantness of the stimulus and were asked to, if needed, re-calibrate it so that the shock still would be "highly unpleasant but not painful". Shocks were administered with an electrical stimulator (Coulbourn Instruments, PA, USA) on the fourth ("ring") and fifth ("pinky") fingers of the non-dominant left hand. During the threat condition, physical shocks were administered on 50% of the trials at the onset of the target display (participants were not informed about the probability of shock).

In this study, my goal was to investigate interactions between appetitive and aversive processing during the preparatory/anticipation period between the cue and target phases, which I refer to as the *delay* phase. To do so, the majority (75%) of trials had a long delay period of 12 s between cue and target phases, unlike most previous studies of the MID task, which have employed short intervals (2-5 sec) (Knutson et al., 2001; Samanez-Larkin et al., 2007). Thus, this design provided a measure of preparatory/anticipation activity that could be largely dissociated from transient events triggered by cue stimuli. During the remaining 25% of trials, a variable delay between 2-10 s was used to prevent subject expectancies from developing; these trials were excluded from the data analysis (see below). The shorter-delay trials also ensured that the onset of the target display (and hence the onset of physical shock when administered) was unpredictable to the participants.

Following the delay, a target display was presented at the center of screen (Fig. 1A). Participants performed a shape discrimination task and were instructed to press the index finger button for circles and the middle finger button for squares with the right hand as fast and accurately as possible. The duration of the target display on each trial was adjusted dynamically (i.e., "staircased") based on the participant's performance. The initial target duration of all conditions was set to the same value and was calibrated for each participant based on a practice run (see below). For each condition, separately, if a correct response was made before the target display disappeared, the target duration on the subsequent trial of that condition was decreased by 34 ms; if an incorrect or slow response was made, the duration was increased by 34 ms. This procedure was employed so that participants would be correct and respond before the target display disappeared, on average, 50% of the time in each condition – thus the task was quite challenging. As noted, during reward trials, reward was based on accurate and fast

performance. Consequently, participants were rewarded on about 50% of reward trials, the same proportion of physical shocks delivered during threat trials.

One second after target onset, participants received visual feedback (1 s) indicating the outcome, as well as their cumulative earnings until that moment. During reward trials, participants won 50 cents per trial if they made a correct response before the target disappeared. On average participants earned $24 (beyond their base pay). During no-reward trials, participants earned zero cents irrespective of their performance. During incorrect or slow-correct trials across all conditions, visual feedback containing the words “incorrect” or “slow”, respectively, was shown. Finally, a 5-10 s variable inter-trial interval (ITI) containing a white fixation cross ended the trial. To minimize the effect of physical shock on the subsequent trial, when a shock was administered, the ITI was set to 10 s.

A practice run was performed during the anatomical scan. No cues were employed (and hence no reward or shock), and visual feedback about correct and incorrect/slow response was provided on each trial. The duration of the target display on the first trial of the practice run was set at 510 ms and was adjusted dynamically in the same fashion as mentioned previously. The final adjusted value was used as the initial duration of the target display for all the conditions in the main task. Participants were not informed that the practice run would be used to calibrate target duration for the main task.

For the presentation of visual stimuli and recording of participant’s responses, Presentation software (Neurobehavioral Systems, Albany, CA, USA) was used. Behavioral responses were collected using an MRI-compatible response box. Skin conductance response (SCR) data were also collected using the MP-150 system (BIOPAC Systems, Inc., CA, USA) with a

10 Hz low-pass hardware filter at a sampling rate of 250 Hz by using MRI-compatible electrodes attached to the index and middle fingers of the left hand.

Each participant performed 12 "runs" of the main task (10 runs for four participants). Each run consisted of 16 trials, resulting in a total of 192 trials and 48 trials per condition (160 and 40, respectively, for four participants). All experimental conditions were intermixed in a pseudorandom fashion.

MR data acquisition

MR data were collected using a 3 Tesla Siemens TRIO scanner (Siemens Medical Systems, Erlangen, Germany) with a 32-channel head coil (without parallel imaging). Each scanning session began with a high-resolution MPRAGE anatomical scan (TR = 1900 ms, TE = 4.15 ms, TI = 1100 ms, 1 mm isotropic voxels, 256 mm field of view). Subsequently, for each functional run, 138 EPI volumes were acquired with a TR of 2500 and TE of 25 ms. Each volume consisted of 44 oblique slices with a thickness of 3 mm and an in-plane resolution of 3 X 3 mm (192 mm field of view). Slices were positioned approximately 30 degrees relative to the plane defined by the line connecting the anterior and posterior commissures, helping to decrease susceptibility artifacts at regions such as the orbitofrontal cortex and amygdala.

General fMRI data analysis

Pre-processing of the data was done using tools from the AFNI software package (Cox, 1996; http://afni.nimh.nih.gov/afni). The first 3 volumes of each functional run were discarded to

account for equilibration effects. The remaining volumes were slice-time corrected using Fourier interpolation, such that all slices were realigned to the first slice to account for timing differences. Six-parameter rigid-body motion correction within and across runs was performed using Fourier interpolation (Cox & Jesmanowicz, 1999), such that all volumes were spatially registered to the first volume. To normalize the functional data to Talairach space (Talairach & Tournoux, 1988), initially, each subject's high-resolution MRPAGE anatomical volume was spatially registered to the so-called TT_N27 template (in Talairach space) using a 12-parameter affine transformation; the same transformation was then applied to the functional data. All volumes were spatially smoothed using a Gaussian filter with a full-width at half maximum of 6 mm (i.e., two times the voxel dimension). Finally, the signal intensity of each voxel was scaled to a mean of 100.

Voxelwise analysis

Each participant's fMRI data were analyzed using multiple regression in AFNI. There were a total of four main event types in the design matrix: no-reward and reward events, separately for the safe and threat conditions. The trials that involved short delay periods (< 12 s) were modeled separately using an additional regressor of no interest (pooled over all four conditions). Constant, linear, and quadratic terms were included for each run separately (as covariates of no interest) to model baseline and drifts of the MR signal. To account for the signal variance related to head motion, six estimated motion parameters were included as nuisance regressors in the model. Given that all three phases (cue, delay, and target) of each trial followed the same sequential order and timing (excluding short delay period trials), I estimated the "combined" trial response. No assumptions were made about the shape of the hemodynamic response

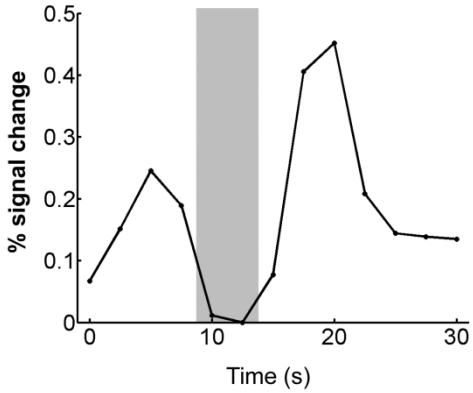

Figure 2. Responses in the visual cortex. Average estimated hemodynamic response (pooled over four conditions) from visual cortex (x = 38, y = -50, z = -17) illustrating that activity at 10 and 12.5 sec post cue onset had minimal contribution from the transient cue phase.

function. Responses were estimated starting from cue onset to 30 s post onset using cubic spline basis functions. This method is closely related to the use of finite impulses ("stick functions"), the commonly employed technique that can be considered the simplest form of basis expansion. Cubic splines allow a smoother approximation of the underlying responses, instead of the discrete approximation obtained by finite impulses. As an index of delay-phase activation, I averaged the estimated responses at 10 and 12.5 s after cue onset (as determined via the spline-based estimates) for all four main event types, separately. I used the average of these two points as the stimulus-*independent* delay-phase response would be maximal at these time points while the effect of transient cue phase responses would be minimal (see Fig. 2 showing visual responses). This method of indexing delay-phase activation is similar to the commonly used method of indexing working memory maintenance- related activity in delayed match-to-sample paradigms (Pessoa et al., 2002; Ranganath & D'Esposito, 2001)

I did not exclude trials containing physical shock as the shock was delivered at the onset of the target display, and the goal of current study was to investigate responses prior to that, namely delay-phase responses.

Group analysis

Whole-brain voxelwise random-effects analyses were restricted to gray-matter voxels based on the FSL automated segmentation tool ["FAST" (FMRIB's Automated Segmentation Tool)] (http://www.fmrib.ox.ac.uk/fsl/). A 2 X 2 repeated-measures ANOVA was run to investigate the interactions between *Reward* (no-reward, reward) and *Threat* (safe, threat) based on delay phase responses. The alpha-level for voxelwise statistical analysis was determined by simulations using the 3dClustSim program of the AFNI toolkit. For these simulations, the smoothness of the data in three directions was estimated using 3dFWHMx on the residual time series of gray-matter voxels in each participant and then averaged across participants (FWHMx = 7.61 mm; FWHMy = 7.63 mm; FWHMz = 7.40 mm). Based on a voxel-level uncorrected alpha of .005, simulations indicated a minimum cluster extent of 34 voxels for cluster-level corrected alpha of .05. I did not analyze the data from cue and target phases because they were possibly contaminated with rising and falling portions of the delay-phase signals, respectively.

Plotting effects for regions of interest (ROIs)

In order to plot the response patterns of the loci showing significant *Reward x Threat* interactions during the delay phase, I carried out an ROI analysis. For each participant, ROIs were defined in an *independent* fashion by using a leave-one-subject-out method. For each subject, I first created 5-mm radius spherical ROIs using the peak voxel locations of the interaction from the 2 x 2 ANOVA based on data from all subjects, except that subject. Then, for each of the four main conditions of interest, delay-phase responses of voxels that showed a significant interaction effect in the "left-out" participants were averaged within the participant's

ROI. I repeated this procedure for each subject and thus was able to plot the interaction pattern for each ROI defined in a non-biased fashion.

Conjunction analysis

In order to identify brain areas activated during the processing of both reward and threat stimuli, I conducted a conjunction analysis (Friston et al., 2005; Nichols et al., 2005), based on delay phase responses. To do so, I initially created two statistical brain masks based on voxels that showed a significant simple effect of *Reward* (reward vs. no-reward during the safe condition; cluster-level alpha: .05) and, separately, a significant simple effect of *Threat* (threat vs. safe during the no-reward condition; cluster-level alpha: .05). I then created an intersection map of these two masks, which revealed voxels with significant common activation.

Skin conductance responses (SCRs)

Skin conductance data from one participant data were excluded due to technical problems during data collection. Data from the remaining participants were initially smoothed with a median-filter over 50 samples (200 ms) to reduce scanner-induced noise and resampled at 1 Hz. The pre-processed SCR data were analyzed using multiple regression in AFNI in a similar way as fMRI data; for related approaches, please see Bach et al.(2009), and Choi et al., (2012). No assumptions were made about the shape of the SCR function. The average response to each trial type was estimated via deconvolution. Variance related to the effect of physical shocks on SCR responses was removed prior to deconvolution. Responses were estimated starting from event onset to 30 s post onset using cubic spline basis functions (see fMRI analysis above for further discussion). Trials that employed a short delay period (< 12 s) were modeled separately using an

additional regressor of no interest (pooled over all four conditions). Constant and linear terms were included for each run separately (as covariates of no interest) to model baseline and drifts of the SCR. As an index of delay response, for each condition, I averaged estimated SCRs between 10-13 s post cue onset (similar time range as used in the imaging data analysis) and subtracted the baseline SCR of each condition (response at cue onset). Finally, in order to help with normality of the data, response-strength indices were transformed by using a logarithm function [$\log_{10}$(1+SCR)]. Then, a 2 X 2 repeated-measures ANOVA was run to investigate interactions between *Reward* (no-reward, reward) and *Threat* (safe, threat).

Behavioral data analysis

Trials during which actual physical shocks were delivered were discarded from the analysis, thus leaving 24 trials in the threat conditions (no-reward and reward) and 48 trials in the safe conditions (no-reward and reward). Trials in which participants made incorrect responses (18%) were excluded from further behavioral analyses, but "slow" trials during which a correct response was made after the target disappeared were included. For each participant, mean RT data were determined as a function of *Reward* (no-reward, reward) and *Threat* (safe, threat). ANOVAs were conducted on the mean RT data, with those variables as within-subject factors. The alpha-level adopted was .05.

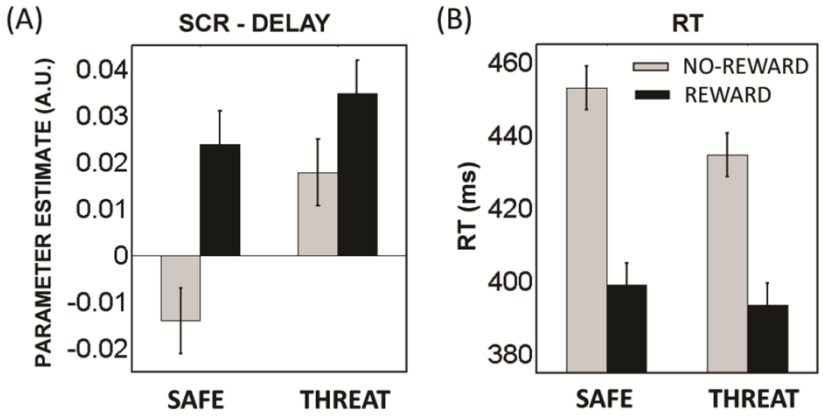

Figure 3. SCR and behavioral results. (A) SCR data during delay phase revealed significant interactions between threat and reward processing, where effect of threat was reduced by reward and effect of reward was reduced by threat. (B) Reaction time data revealed a marginally significant interaction between threat and reward. Error bars in all panels denote the standard within-subject error term (Loftus & Masson, 1994) for the two-way interaction. A.U., arbitrary units.

Results

Skin Conductance Responses

Skin conductance responses (SCRs) during the delay phase were evaluated according to a 2 *Reward* (no-reward, reward) x 2 Threat (safe, threat) repeated-measures ANOVA. The main effects of *Threat* and *Reward* were significant ($F_{1, 19}$ = 11.79, p = .0028 and $F_{1, 19}$ = 5.84, p = .0259, respectively). SCR was greater during threat compared to safe trials, as well as during reward compared to no-reward trials. Notably, a statistically significant *Reward x Threat* interaction was obtained ($F_{1, 19}$ = 6.43, p = .0202), such that the increased SCR during threat (vs. safe) trials during the no-reward condition was reduced during reward and the increased SCR during reward (vs. no-reward) during the safe condition was reduced during threat (Fig. 3A).

Behavioral results

Mean RT data were evaluated according to a 2 *Reward* (no-reward, reward) x 2 Threat (safe, threat) repeated-measures ANOVA (Fig. 3B). The main effect of *Reward* was significant ($F_{1, 19}$ = 49.02, p = .0001). Mean RT was faster during the reward (395 ms) compared to the no-reward condition (444 ms), demonstrating the effectiveness of the motivational manipulation. The threat condition also showed faster responses (414 ms) compared to the safe (425 ms) condition, revealing a main effect of *Threat* ($F_{1, 19}$ = 13.88, p = .0014). It is possible that, although threat was irrelevant to the task, cues signaling shock might have increased arousal (as indicated by SCR data), which might have speeded motor responses. The *Reward x Threat* interaction was marginally significant ($F_{1, 19}$ = 3.52, p = .0761). This trend-level result was observed given that faster RTs during reward relative to no-reward trials during the safe condition (56 ms) were numerically reduced during the threat condition (43 ms).

Functional MRI results

The main goal of this study was to investigate interactions between appetitive and aversive processing during the anticipatory/delay phase. Accordingly, I ran a 2 *Reward* (no-reward, reward) x 2 *Threat* (safe, threat) voxelwise repeated-measures ANOVA based on estimated responses of the delay phase. I observed a main effect of *Reward* in several structures, including dorsal ACC and, bilaterally, midbrain/ventral tegmental area (VTA), caudate, putamen, nucleus accumbens, and anterior insula; in all cases, responses during reward were greater than no-reward (Table 1). I also observed a main effect of *Reward* in "default" brain regions (Raichle et al., 2001), where responses decreased during reward (vs. no-reward). A main effect of *Threat*

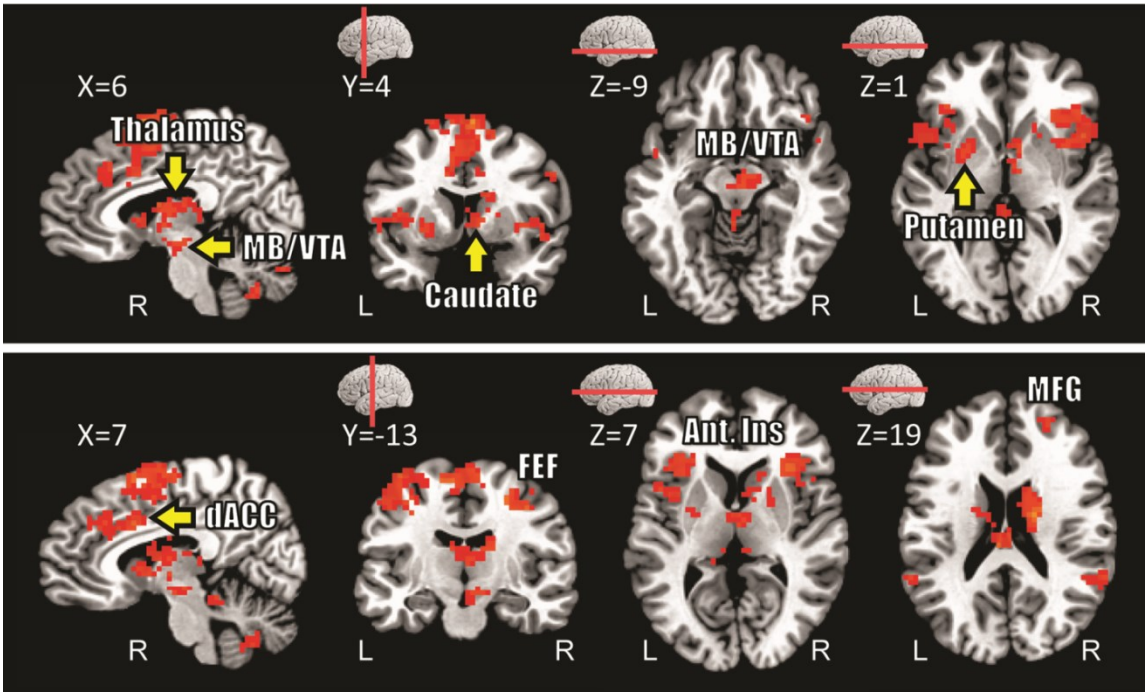

Figure 4. Delay phase responses. Voxels that showed significant interaction between threat and reward (displayed at $p < 0.05$, cluster-level corrected). MB/VTA, midbrain/ventral tegmental area; dACC, dorsal anterior cingulate cortex; Ant. Ins, anterior insula; FEF, frontal eye field; MFG, middle frontal gyrus.

was observed in dorsal ACC, bilateral middle frontal gyrus (MFG), left inferior frontal cortex, and right inferior fontal cortex extending into the anterior insula; in all cases, responses during threat were greater than during safe. Critically, a significant interaction between *Reward* and *Threat* was observed in the right midbrain/VTA, right caudate, bilateral putamen, bilateral thalamus, bilateral frontal eye field, bilateral anterior insula, right MFG, and dorsal ACC (Fig. 4). As illustrated in Fig. 5A, a trade-off between reward and threat processing was observed in the right midbrain/VTA, such that the effect of reward (reward vs. no-reward) during the safe condition was reduced during threat; likewise, the threat effect (threat vs. safe) during no-reward was reduced during reward. Note that, although the coordinates of the midbrain site I report are consistent with the VTA (Adcock et al., 2006; Carter et al., 2009), given the spatial resolution of the fMRI signal, spatial smoothing, and size of this structure, this label should be interpreted as "suggestive". For additional regions, see also Figure 5B-5D & 6A-6D.

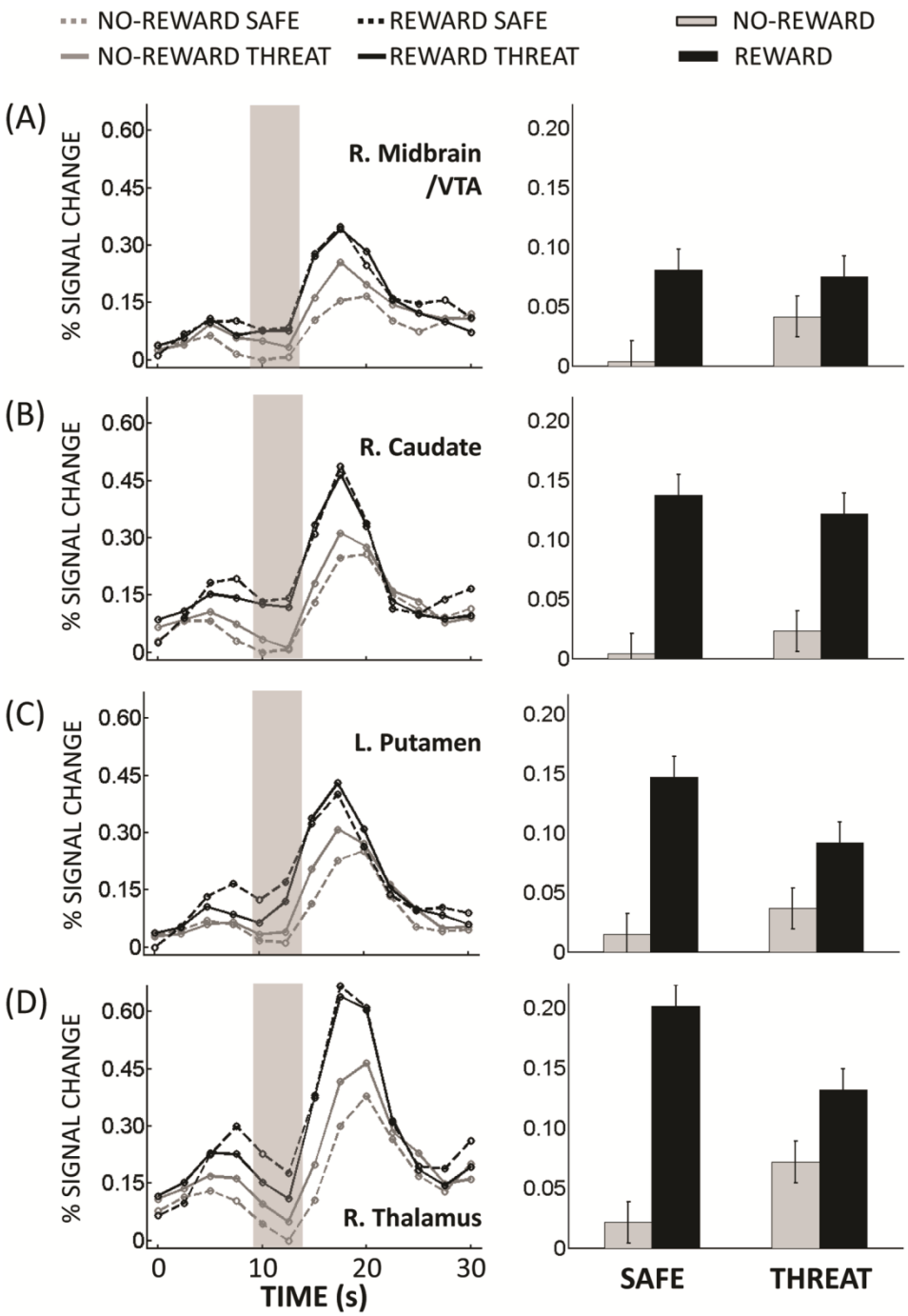

Figure 5. Delay phase responses. (A) Mean estimated hemodynamic responses from the right midbrain/VTA ROI (left panel), where the gray area indicates delay-phase responses. On the right panel, these responses are shown as a bar plot (B) Right ventral caudate ROI. (C) Left Putamen ROI. (D) Right thalamus ROI. Error bars in bar plots denote the standard within-subject error term (Loftus & Masson, 1994) for the two-way interaction.

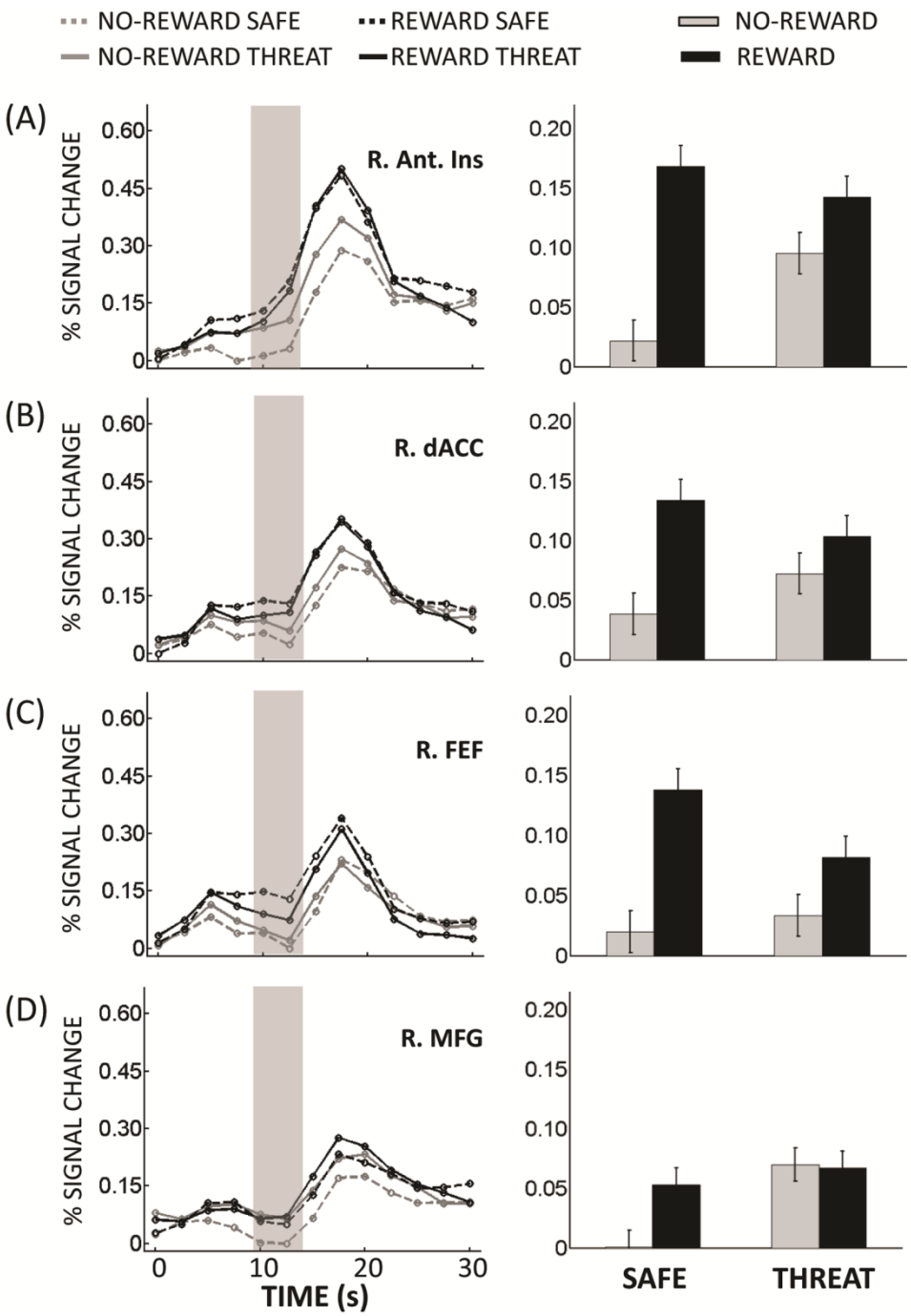

Figure 6. **Delay phase responses.** (A) Mean estimated hemodynamic responses from the right anterior insula ROI (left panel), where the gray area indicates delay-phase responses. On the right panel, these responses are shown as a bar plot (B) Dorsal anterior cingulate cortex ROI. (C) Right frontal eye field ROI. (D) Right middle frontal gyrus ROI. Error bars in bar plots denote the standard within-subject error term (Loftus & Masson, 1994) for the two-way interaction.

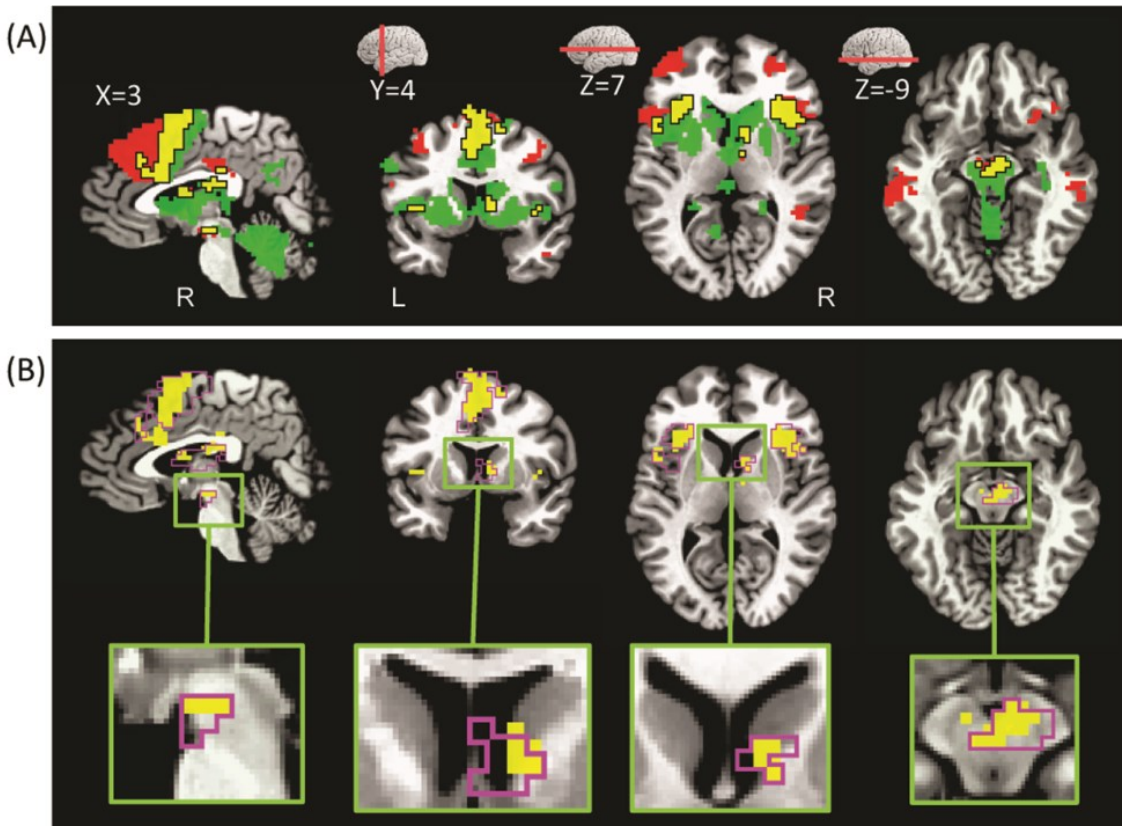

Figure 7. **Conjunction analysis at delay phase.** (A) Voxels that showed significant common activation during threat (vs. safe during no-reward) and reward (vs. no-reward during safe) are shown in yellow color. For illustrative purposes only (with no inferential interpretations), voxels that showed significant activation during threat (vs. safe during no-reward) but not in reward (vs. no-reward during safe) are shown in red color. In a similar fashion, voxels that showed significant activation during reward (vs. no-reward during safe) but not in threat (vs. safe during no-reward) are shown in green color. (B) Voxels that showed significant common activation during threat (vs. safe during no-reward) and reward (vs. no-reward during safe) are shown in yellow color and the border of the clusters that exhibited significant *Reward* x *Threat* interactions are shown in magenta color.

Control analysis

In the results reported above, delay-phase responses might have been partly confounded with motor preparatory signals associated with the target phase. One way to partially address this possibility is to investigate the role of RT in the observed responses. Accordingly, I repeated the analysis above, but now including an additional parametric RT regressor (mean corrected). I

reasoned that this additional regressor would model variance related to fluctuations in motor preparation across trials as indexed by RT values. Importantly, this control analysis also revealed significant *Reward* x *Threat* interactions in all the regions reported above, minimizing the possibility that the interaction effects were largely driven by changes in motor preparation across conditions.

Conjunction analysis

To identify brain regions commonly engaged by reward and threat processing, a conjunction analysis was run based on delay-phase responses of simple reward and simple threat effects. The conjunction analysis revealed clusters of common activation in several brain regions, notably, right midbrain/VTA, right ventral caudate, right thalamus, bilateral anterior insula, dorsal ACC, and bilateral MFG (Fig 7; Table 2). I also inspected the consistency of the simple effects in individual participants as, in theory, there could be clusters of common activation at the group level without a clear counterpart in the individuals. For each region, I list the number of participants exhibiting the two simple effects (final column in Table 2), indicating that the conjunction did not originate from the group analysis process.

Amygdala ROI analysis

In the above analyses, I did not observe significant results in the amygdala. But given the theoretical importance of the amygdala in emotional processing, I conducted an additional ROI analysis to probe the signals of this area. Left and right amygdala ROIs were defined based on

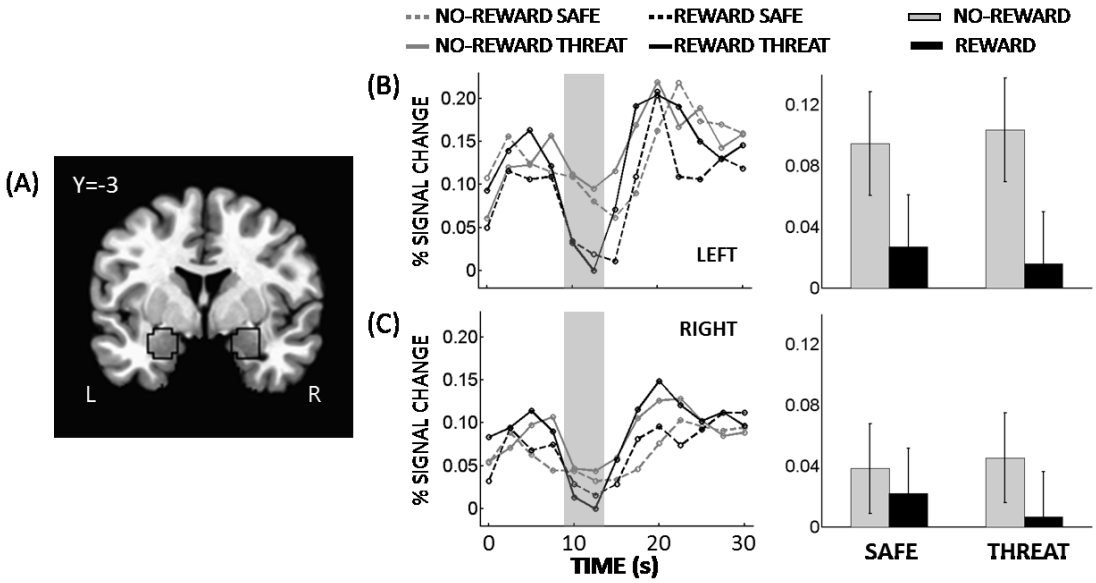

Figure 8. Responses in the amygdala. (A) Coronal slice of the TT_N27 template brain in AFNI showing the voxels within the anatomically defined amygdala (black outline). (B) Mean estimated hemodynamic response functions of four conditions from the left amygdala ROI. (C) Mean estimated hemodynamic response functions of four conditions from the right amygdala ROI. In B and C, the gray area indicates the response estimates related to delay phase. Error bars in bar plots denote the standard within-subject error term (Loftus & Masson, 1994) for the two-way interaction.

anatomy (Fig. 8A). In each ROI, a representative time series was created by averaging the unsmoothed time series from all gray-matter voxels within the ROI. Then, as in the whole-brain voxelwise analysis, multiple regression was run on the representative time series data to estimate the hemodynamic response function of four main regressors of interest. A 2 X 2 repeated-measures ANOVA was then run to probe potential interactions between *Reward* (no-reward, reward) and *Threat* (safe, threat). Analysis of delay-phase data revealed only a significant main effect of *Reward* in the left amygdala ROI, such that responses were reduced during reward compared to no-reward (Table 3; Fig. 8B-8C).

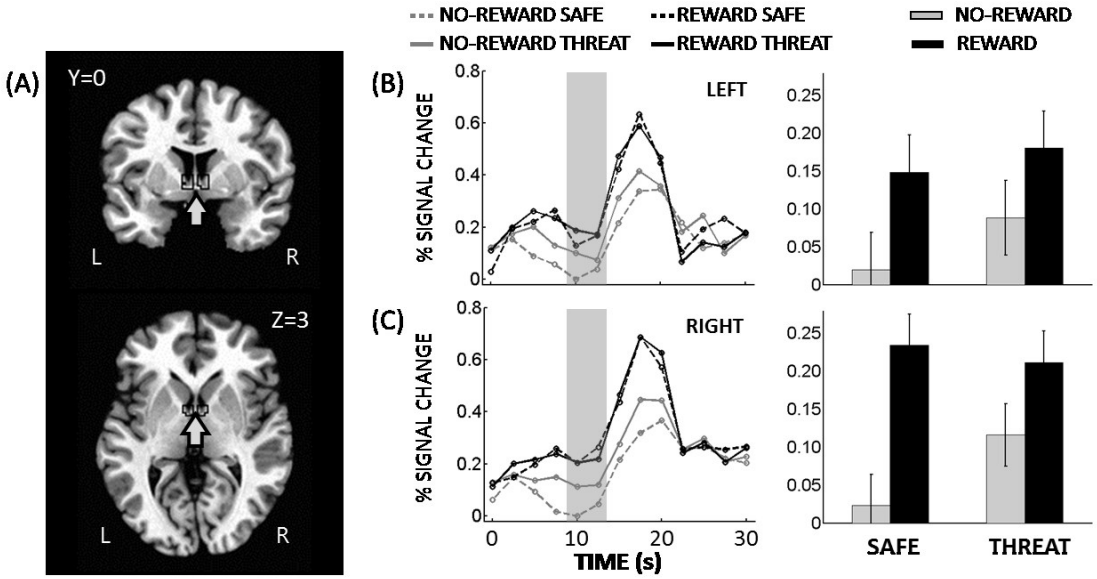

Figure 9. Responses in the BNST. (A) Coronal and axial slices of the TT_N27 template brain in AFNI showing the voxels within the anatomically defined BNST (black outline). (B) Mean estimated hemodynamic response functions of four conditions from the left BNST ROI. (C) Mean estimated hemodynamic response functions of four conditions from the right BNST ROI. In B and C, the gray area indicates the response estimates related to delay phase. Error bars in bar plots denote the standard within-subject error term (Loftus & Masson, 1994) for the two-way interaction.

BNST ROI analysis

I also investigated basal forebrain sites consistent with the BNST, a structure implicated in anxiety-related mechanisms (Davis, et al., 2010). In the whole-brain voxel-wise analysis reported previously, the ventral caudate cluster posteriorly extended into the basal forebrain. Given that the BNST is a small region and the voxel-wise analysis was done on spatially smoothed data, I conducted an additional ROI analysis. Left and right BNST ROIs were defined anatomically according to the atlas of Mai et al., 1997 (see also Alvarez et al., 2011, Fig. 9A). Talairach x-values were restricted between 3 and 8 mm, y-values were restricted between -1 and 3 mm, and z-values were restricted between -1 and 6 mm. For this analysis, I resampled the functional data to a finer 2 x 2 x 2 mm voxel grid and no spatial smoothing was applied. For each ROI, a

representative time series was created by averaging the unsmoothed time series from all the gray-matter voxels that fell inside the anatomically defined ROI. Then, regression analysis was run to estimate condition-specific responses. A 2 X 2 repeated-measures ANOVA was subsequently run to probe potential interactions between *Reward* (no-reward, reward) and *Threat* (safe, threat). Analysis of delay-phase data revealed a main effect of *Reward* in both BNST ROIs, such that responses were increased during reward compared to no-reward; and a main effect of *Threat* in the left BNST ROI, such that responses were increased during threat compared to safe. Critically a significant interaction between *Reward* and *Threat* was observed in the right BNST (Table 4; Fig. 9B-9C), such that the effect of reward was reduced during threat and the effect of threat was reduced during reward. The right BNST ROI also showed simple effects of both *Reward* (reward vs. no-reward during the safe condition: $t(19) = 5.11$, $p = .0001$) and *Threat* (threat vs. safe during the no-reward condition: $t(19) = 2.67$, $p = .014$).

Discussion

To investigate the interactions between appetitive and aversive processing, I used a task with cues signaling the chance of monetary reward and/or mild aversive shock. The experimental design allowed me to measure responses during the preparatory/anticipatory delay phase with minimal contamination from other task phases, thus enabling me to probe stimulus-independent processes. SCR data revealed interactions between reward and threat during the delay phase. Imaging data during this phase revealed interactions between reward and threat in several key brain regions, including the midbrain/VTA, striatum, BNST, anterior insula, right MFG, and dorsal ACC. Overall, the results support the competition hypothesis and not the salience

hypothesis: when reward and threat were jointly present, reward opposed the effect of threat ($[\text{threat vs. safe}]_{\text{REWARD}} < [\text{threat vs. safe}]_{\text{NO-REWARD}}$) and threat opposed the effect of reward ($[\text{reward vs. no-reward}]_{\text{THREAT}} < [\text{reward vs. no-reward}]_{\text{SAFE}}$).

Midbrain structures and the striatum are engaged by appetitive processing (Delgado, 2007; Haber & Knutson, 2010). But recruitment of these regions is not limited to appetitive conditions. They take part in the processing of aversive stimuli (Baliki et al., 2010; Becerra et al., 2001; Brischoux et al., 2009; Matsumoto & Hikosaka, 2009; Roitman et al., 2005), financial losses (Carter, et al., 2009), anticipation of mild shocks (Jensen et al., 2003), and aversive learning (Delgado et al., 2008). The engagement of these regions during both positive and negative contexts has led to the idea of their role in "motivational salience" (Carter, et al., 2009; Jensen, et al., 2003; Jensen et al., 2007; Metereau & Dreher, 2012). The results in current study demonstrated instead that simultaneous reward and threat information opposed each other. Together, the findings demonstrated competition during the processing of motivationally salient stimuli of opposite valence. Of note, when presented alone, appetitive and aversive cues evoked delay-phase responses in the midbrain and striatum (Fig. 7A).

In the nucleus accumbens, consistent with prior studies (Knutson, et al., 2001; Schultz et al., 1992), a main effect of *Reward* was observed during the delay phase. But, neither a main effect of *Threat* nor an interaction was observed. The absence of a threat effect was somewhat unexpected given the rodent literature (Roitman, et al., 2005; Schoenbaum & Setlow, 2003). Nevertheless, the results are consistent with some studies in humans that did not observe accumbens activation during anticipation of mild shocks (Choi, et al., 2012) and aversive pictures (Grupe et al., 2012). Future studies using other types of aversive conditions, such as monetary

losses (Carter, et al., 2009), are needed to clarify potential interactions between appetitive and aversive processing in this region.

The anterior insula is involved during the processing of negative events, such as cues signaling monetary losses (Knutson & Greer, 2008), as well as the anticipation and experience of aversive stimuli (Paulus & Stein, 2006; Simmons et al., 2006). The anterior insula also has been implicated in risk aversion (Kuhnen & Knutson, 2005). Yet, recent studies have observed activation in this region during appetitive processing, including to cues signaling monetary gains (Liu, et al., 2011; Padmala & Pessoa, 2011; Samanez-Larkin, et al., 2007). Furthermore, anterior insula neurons increased responses when monkeys knew they would, or might receive, a reward based on performance (Mizuhiki, et al., 2012). Here, I also observed the effect of reward and threat in the bilateral anterior insula during the delay phase (Fig. 7A). Critically, threat and reward processing opposed each other when simultaneously presented.

I did not observe a main effect of *Threat* or an interaction in the amygdala during the delay phase. This null finding is not entirely surprising because, as proposed by Davis, Grillon, and colleagues (2010), responses in the amygdala may be more closely tied to phasic CS+ stimuli signaling "fear" or transient cues that signal aversive stimuli (Grupe, et al., 2012), as opposed to the periods of temporally extended and less predictable threats. Of note, in my previous study (Choi, et al., 2012), as well as in a study by Somerville and colleagues (2010), greater amygdala responses were *not* detected during threat monitoring over a temporally extended period.

Another region that is involved in threat processing is the BNST in the basal forebrain, especially during conditions involving temporally extended and/or less predictable threat (Alvarez, et al., 2011; Davis, et al., 2010; Somerville et al., 2013; Somerville, et al., 2010).

Intriguingly, studies have also reported the involvement of BNST in appetitive processing (McGinty et al., 2011). This region, which is small and has a complex anatomy, is challenging to investigate with functional MRI. Here, I investigated BNST responses based on an anatomical ROI and unsmoothed data. The right BNST was activated by both threat and reward during the delay phase. In addition, a significant interaction was detected there during the delay phase, such that reward and threat traded-off against each other.

In the context of aversive processing, the thalamus has been reported to be involved during the anticipation and experience of negative picture stimuli (Goldin et al., 2008; Herwig et al., 2007), anticipation of mild aversive shocks (Choi, et al., 2012)and pain processing (Casey, 1999). At the same time, however, the thalamus participates in appetitive motivational circuits together with striatal and midbrain regions (Kalivas & Nakamura, 1999). The involvement of the thalamus in appetitive processing is further supported by human imaging studies with monetary incentives (Engelmann et al., 2009; Galvan et al., 2005; Knutson, et al., 2001) and related studies in nonhuman animals (Balleine, 2005; Gaffan & Murray, 1990; Minamimoto et al., 2005). In the current study, delay-phase responses in the thalamus were observed during threat as well as reward (Fig. 7A). In addition, I observed a significant interaction between reward and threat during the delay phase where reward and threat competed against each other when presented simultaneously.

The dorsal ACC participates in both appetitive and aversive processing, especially during goal-directed behaviors, suggesting that it plays an important function in “adaptive control” (Rushworth & Behrens, 2008; Shackman et al., 2011b). Many studies have reported dorsal ACC responses to reward (Bush et al., 2002; Shidara & Richmond, 2002; Shima & Tanji, 1998) and threat (Etkin et al., 2011; Ploghaus et al., 1999) stimuli. Here, dorsal ACC responses during the

delay phase revealed simple effects of reward (vs. no-reward during the safe condition) and threat (vs. safe during the no-reward condition). Again, a competitive interaction between reward and threat was observed during the delay phase.

Whereas the dorsolateral PFC is important for cognition in general, it also has been proposed to be an important convergence site for the integration of both motivation and cognition (Kobayashi et al., 2002; Leon & Shadlen, 1999; Watanabe, 1996) and emotion and cognition (Erk et al., 2007; Gray et al., 2002). In a consistent fashion, here I observed an interaction between reward and threat processing in the right MFG during the delay phase such that reward and threat traded-off against each other.

I also observed a trade-off interaction in the frontal eye field (FEF), bilaterally, during the delay phase. In addition, the FEF showed a main effect of *Reward*. These findings are intriguing because the FEF is important for attention (Armstrong et al., 2006; Corbetta & Shulman, 2002; Kastner & Ungerleider, 2000; Moore & Armstrong, 2003). I interpret the main effect of *Reward* in terms of attention given that, upon seeing the reward cue, participants likely up-regulated attention (as indicated by faster RTs). If this interpretation is correct, the counteracting effect of threat on FEF responses suggests that threat might have interfered with attention. In any case, the interaction reveals that reward and threat interact in frontal sites that are important for attention and other related cognitive functions.

Competition

The interaction effect in current study revealed a trade-off between reward and threat processing consistent with competitive interactions. Notably, voxels exhibiting the interaction

overlapped with those exhibiting simple effects of both reward and threat (Fig. 7B), revealing that many of the areas influenced by both reward and threat are also sites of competitive interactions.

The trade-off pattern observed here is consistent with several independent lines of studies. For example: reward and pain signals interacted in the calculation of subjective value underlying behavioral choice (Park, et al., 2011); pain reduced reward sensitivity during a decision making task (Talmi, et al., 2009); stress reduced reward-related responses in medial PFC (Ossewaarde et al., 2011); and acute stress decreased reward responsiveness (Bogdan & Pizzagalli, 2006) and reward outcome responses (Porcelli et al., 2012). In particular, the reduction of the threat effect during reward in current study is consistent with findings from the startle reflex, where blink responses are reduced during anticipation of rewards (Hackley et al., 2009; see also Lang et al., 1998).

Why is the trade-off pattern observed in the present study? A possible reason is because reward was task relevant while threat might have functioned as a “distractor”. In this way, they might have acted against each other in a way that can be recast in terms of competition for limited processing resources (Pessoa, 2009). This explanation is attractive when sites such as the FEF are considered given their association with attention. The explanation is less appealing, perhaps, when regions such as the midbrain are concerned. Although some researchers have proposed that these regions can also be viewed as associated with “effort” (Boehler et al., 2011; Horvitz, 2000; Salamone et al., 2009), it is possible that the trade-off reflected the organization of positive and negative systems into opponent motivational systems (Konorski, 1967; Solomon & Corbit, 1974), which would operate in a push-pull fashion. Note, however, that the current experiment was not designed to arbitrate between these two

scenarios as reward was contingent on performance but shock was not. I used this asymmetric design to evaluate the salience and competition hypotheses, and not different types of competition mechanisms.

In conclusion, using a factorial design, I investigated stimulus-independent interactions between processing of appetitive and aversive stimuli in normal healthy adult volunteers. The results from SCR data revealed a trade-off between reward and threat processing. Paralleling the SCR data, imaging data also revealed a trade-off pattern in regions such as midbrain, striatum, BNST, anterior insula, right MFG and dorsal ACC, revealing conditions during which reward and threat compete in the brain when processed simultaneously.

Table 1. Voxelwise analysis at delay phase (Peak talairach coordinates, *F(1,19)* and *t(19)* values)

		Reward x Threat					***Reward***					***Threat***			
Peak Location		*x*	*y*	*z*	*F*		*x*	*y*	*z*	*t*		*x*	*y*	*z*	*t*
Occipital															
Middle occipital gyrus	L											-40	-64	2	-5.67
	R											37	-71	2	-3.87
Temporal															
Fusiform gyrus	R											41	-49	-10	-4.54
Parahippocampal gyrus	L						-25	-43	-7	-4.54		-25	-37	-10	-5.45
	R						20	-38	-7	-3.51		11	-46	-7	-4.78
Superior temporal gyrus	R											50	-28	20	5.19
Middle temporal gyrus	L											-64	-34	-7	5.39
	R											53	-31	-7	5.45
	L						-49	-67	26	-5.66					
	R						41	-70	23	-4.59					
Parietal															
Posterior cingulate cortex	L						-7	-52	26	-6.63					
Precuneus	L											-13	-67	29	4.36
Supra marginal gyrus	L	-55	-52	32	28.39							-52	-49	29	5.89
	R	47	-49	29	45.51							56	-58	26	5.82
Inferior parietal lobe	L	-37	-34	32	20.53		-43	-34	38	5.52					
Left precentral gyrus	L						-40	-19	56	7.01		-52	-13	35	-4.07
	R	47	-1	32	21.51		44	-4	50	5.35					
Mid-cingulate cortex												-1	-28	29	4.99
Frontal															
Frontal eye field	L	-19	-7	50	28.06		-28	-10	44	4.74					
	R	25	-10	44	32.82		26	-13	44	4.49					
Supplementary motor area	L	-10	-10	56	51.66		-7	-7	50	5.52		-4	20	50	6.18
	R	5	11	59	58.28		14	-1	56	5.62		8	18	55	5.07
Middle frontal gyrus (posterior)	L											-34	8	44	4.55
	R											41	14	38	6.79
Middle frontal gyrus (anterior)	L											-22	47	26	4.95
	R	23	41	17	23.11							20	41	26	6.00
Inferior frontal gyrus	L											-52	23	14	9.17
	R											50	20	14	4.86
Anterior cingulate cortex (dorsal)	L						-7	5	38	4.72		-4	26	32	5.61
	R	8	11	32	43.38		8	5	38	7.10					
Superior medial frontal gyrus							-7	56	14	-5.24					
Posterior insula	R						35	-16	17	-4.94					
Mid-insula	L	-43	8	5	22.14		-43	5	8	4.07					
	R	47	8	-1	30.76		38	8	5	4.75					
Anterior insula	L	-31	26	5	27.04		-31	20	11	6.88					
	R	32	20	8	40.34		29	20	11	7.17		47	20	-1	4.15

	R	29	14	-4	28.46										
Subcortical															
Midbrain/Ventral tegmental area	L						-10	-16	-13	4.72					
	R	8	-19	-7	22.3		11	-13	-10	5.41					
Thalamus	L	-5	-8	10	16.04										
	R	5	-8	11	19.6		5	-13	-1	4.90					
Putamen	L	-22	2	-1	21.92		-25	-1	11	6.59					
	R	20	2	8	12.91		23	-1	11	5.42					
Caudate	L						-10	8	2	5.41					
(dorsal)	R	17	-7	20	45.42		20	5	17	6.26					
(ventral)	R	8	5	5	22.16		8	2	2	7.17					
Nucleus Accumbens	L						-10	10	2	5.15					
	R						10	10	2	5.84					
Cerebellum	L	-19	-61	-31	32.51		-34	-43	-28	5.72					
	L	-13	-79	-19	25.01		17	-46	-19	6.44					
	R	29	-55	-25	19.71		23	-46	-46	5.86					

Table 2. Conjunction analysis at delay phase (Peak talairach coordinates of minimum *t(1,19)* values)

Peak location		*x*	*y*	*z*	*t*	*
Parietal						
Supra marginal gyrus	L	-52	-43	23	4.25	15
	R	56	-43	20	5.11	15
Precentral gyrus	R	35	-7	38	4.67	15
Frontal						
Supplementary motor area	R	2	5	50	4.82	17
Anterior cingulate cortex (dorsal)	R	5	11	35	5.59	16
	R	5	29	35	4.86	13
Middle frontal gyrus	L	-34	44	29	3.94	13
	R	29	47	20	4.49	15
Anterior insula	L	-31	23	11	5.49	16
	R	32	20	8	6.30	17
Subcortical						
Thalamus	R	8	-13	-1	4.15	15
Caudate	R	8	5	5	4.30	14
Ventral tegmental area	R	8	13	-7	4.86	14
Cerebellum	L	-25	-61	-31	4.29	15
	L	-40	-49	-31	4.34	15
	R	26	-67	-25	3.56	14

*number of participants with both simple effects of reward and threat

Table 3. ROI analysis in Amygdala based on delay-phase responses

ROI	Left Amygdala			Right Amygdala	
	F(1,19)	*p*		*F(1,19)*	*p*
Main effect of *Reward*	6.63	0.019		1.36	0.258
Main effect of *Threat*	0.00	0.996		0.25	0.621
Reward x *Threat*	0.02	0.892		0.27	0.612

Table 4. ROI analysis in BNST based on delay-phase responses

ROI	Left BNST			Right BNST	
	F(1,19)	*p*		*F(1,19)*	*p*
Main effect of *Reward*	7.39	0.014		22.77	0.000
Main effect of *Threat*	5.85	0.026		2.25	0.150
Reward x *Threat*	0.421	0.524		8.67	0.008

CHAPTER 3: Interaction between threat and aversive processing

Introduction

Motivation is one of the major determinants which influence behavior via “energization” (Elliot, 2006) and/or “motivational salience” (Zink et al., 2004). Motivation can be divided into two aspects. One is appetitive (or approach), and the other is aversive (or avoidance) motivation (Elliot&Covington, 2001 for review). The appetitive motivation drives an organism toward appetitive stimuli/outcome (i.e. reward) whereas the aversive motivation makes an organism to withhold action or to get away from aversive stimuli/outcome (i.e. punishment).

In neural mechanism of motivational processing, midbrain and striatum play a key role. Supporting evidence can be found in the studies using lesion and pharmacological manipulation (Parkinson et al., 2000; Cardinal et al., 2002; Smith&Dickinson, 1998; Taylor & Robbins, 1984; Cador et al, 1991). However, it is unclear that this “reward circuitry” is specific to reward-predicting stimuli, or to punishment-predicting stimuli as well. In the animal literature, Matsumoto and Hikosaka (2009) showed that some dopaminergic neurons in the midbrain of monkeys respond to airpuff-predicting stimuli as well as reward-predicting stimuli. In addition, in rats, a set of neurons in ventral striatum were found to respond during quinine as well as sucrose anticipation, whereas another set of neurons only responded during sucrose anticipation (Bissonette et al., 2013).

Some human imaging studies have reported that reward-related regions such as ventral striatum were also involved during punishment anticipation with monetary losses (Carter et al., 2009; Cooper and Knutson, 2008; Wu et al., 2014) or electric shock (Jensen et al., 2003). However, other studies reported that the neural substrates in the ventral striatum were altered depending on the valence of the reinforcement (reward or punishment) in terms of the

activation level (Tom et al, 2007) or location (Seymour et al, 2007). Finally, it has been reported that anterior insula and dorsal ACC are engaged by processing loss aversion (Fujiwara et al., 2009; Kuhnen and Knutson, 2005; Paulus et al., 2003).

The previous experiment in Chapter2 examined interactions between threat and reward. Analysis of SCR during delay period showed that the reward anticipation response was reduced under threat of shock. Imaging data during same period also revealed the interaction between threat and reward in several brain regions, including midbrain/VTA, striatum, BNST, anterior insula, right MFG, and dorsal ACC. The results suggest that reward and threat processing compete against each other. However, it is not clear which competition mechanism is involved in the interaction. One possibility is that, threat anticipation functioned as a "distractor". According to dual-competition model (Pessoa, 2009), threat processing competes with cognitive processing for limited attentional resources. If threat processing used attentional resources, cognitive processing would be compromised. Given that reward enhances attentional control, cognitive control would experience a reduced reward effect under threat of shock. Alternatively, the competitive interaction effect might be due to opponent processing between threat and reward (Konorski, 1967; Solomon & Corbit, 1974). Thus, when both appetitive and aversive outcomes are expected (electric shock and monetary incentives), the intensity of a stimulus might be reduced by another stimulus having opponent valence. However, the results in Chapter 2 do not distinguish which of the competition mechanisms was involved because appetitive outcome (reward) depended on task performance but aversive outcome (electric shock) did not.

To further investigate the competition mechanisms between threat and reward, a punishment condition was included in current study. Like reward, punishment can motivate behaviors in a way of leading an organism to avoid the aversive outcome. By adding punishment

condition, I could manipulate motivational valence (appetitive vs. aversive motivation) while mostly controlling motivational arousal.

Like the experiment in Chapter 2, I used a variant of the monetary incentive task (Fig. 10A; Knutson et al., 2000). During the task, six types of visual cues were presented (Fig. 10B). The visual cues can be divided into two types. Threat cue informed participants about possibly receiving a mild electric shock which was independent on performance. Motivation cue (reward or punishment cues) informed them about the chance of winning or losing monetary incentives depending on their task performance. Thus, participants were motivated by reward and punishment cues to maximize winning and minimize losing the incentives.

I tested two competing hypotheses in key brain regions, including the midbrain, striatum, anterior insula, and dorsal ACC. According to the "resource hypothesis", threat processing would utilize attentional resources which are necessary for other executive functions. Consequently, the impact of punishment on goal-directed processing would be reduced. Thus, responses during punishment anticipation would be decreased with threat compared to safe, just like reward responses under threat of shock. In contrast, according to the "valence hypothesis", aversive motivation would be enhanced under threat whereas appetitive motivation would not be reduced. Thus, responses during punishment anticipation would be increased in threat compared to safe condition, whereas responses during reward anticipation would be decreased in threat compared to safe.

Materials and Methods

Subjects

Thirty volunteers participated in the study, which was approved by the Institutional Review Board of the University of Maryland, College Park. Based on self-report, subjects were free from psychiatric or neurological disease or related past history. All participants were right-handed, had normal or corrected-to-normal vision, and gave informed written consent. Three participants' data were excluded from the analysis because of head motion exceeding 3 mm. Two other participants' data were also excluded because of poor performance (over 25% error rates in general) compared to others (9.40%±4.25). Thus, data from twenty five participants (27.92±4.61 years old; 12 females) were included in the final analysis.

Stimuli and behavioral paradigm

Each trial started with the presentation of a visual cue stimulus (1 s), which was followed by 2 – 6 s variable delay period (Fig. 10A). The visual cue was either rectangle- or diamond-shaped (safe or threat). A dollar or exclamation sign, or none of it was included in the geometric shape. The dollar and exclamation signs indicated the reward and punishment conditions, respectively. In control condition (no-reward and no-punishment), none of them was shown. The geometric shape (rectangle or diamond) indicated the Threat condition (safe or threat). Thus, six different types of cues were used (Fig. 10B). The dollar sign indicated the chance of winning monetary reward if the response was made correctly before the display disappeared. The exclamation sign indicated the risk of losing some of reward which was accumulated during the experiment if the response was incorrect or made after the display disappeared. The geometric shape (which was

counterbalanced across participants), indicated that a mild electric shock could be delivered before the onset of the target display (independent of performance). During the threat condition, physical shocks were administered 0.5 s earlier than target onset on 33% of threat trials. Participants were not informed about the probability of shock, and the shock timing was varied (1.5 – 5.5 s) after offset of threat cue. Thus, the shock administration was fairly unpredictable. To calibrate the intensity of the electric shock, each participant was asked to choose his/her own stimulation level immediately prior to functional imaging, such that the stimulus would be "highly unpleasant but not painful". After each run, participants were asked about the unpleasantness of the stimulus and were asked to, if needed, re-calibrate it so that the shock still would be "highly unpleasant but not painful". Shocks were administered with an electrical stimulator (Coulbourn Instruments, PA, USA) on the fourth ("ring") and fifth ("pinky") fingers of the non-dominant left hand.

After delay period, a target display (0.69s) was presented at the center of screen. Participants were instructed to discriminate expression of a face target by pressing the index or middle finger button for neutral or fearful faces with the right hand as fast and accurately as possible (response button was counterbalanced). The duration of the target display was determined based on pilot study[1]. As noted, during reward and punishment trials, monetary gain and loss were based on accurate and fast performance. Consequently, participants were rewarded on about 87.7% of reward trials, and avoided punishment about 84.3% of punishment trials.

[1] In the pilot study, 16 participants performed facial expression discrimination task (fearful vs safe) with "stair-casing" procedure. Mean value of last 15 trials + 1 standard deviation was used for RT threshold in order to have over about 70% on control trials.

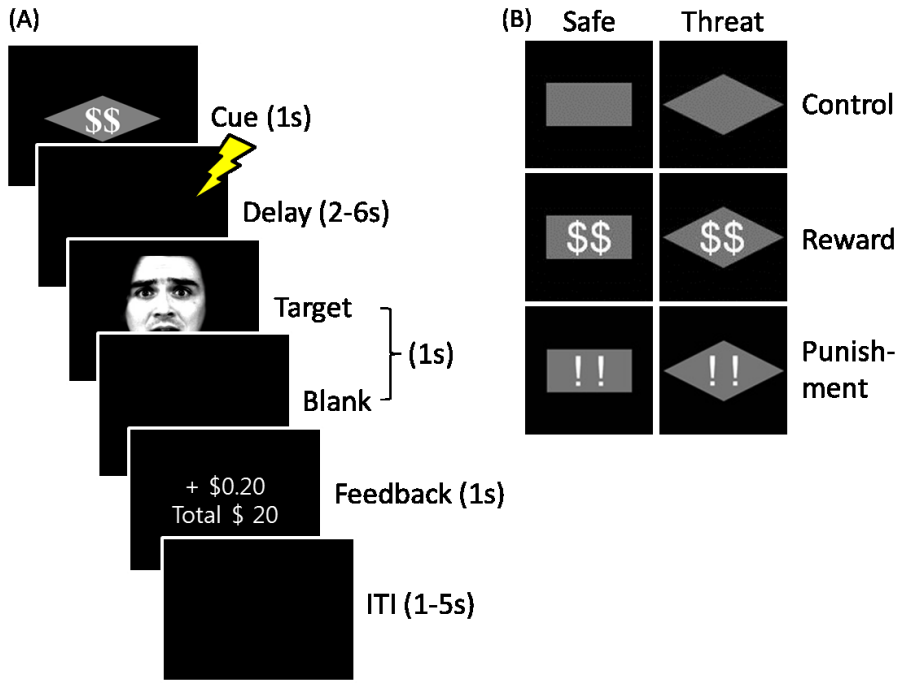

Figure 10. Task design. (A) Subjects performed a variant of Monetary Incentive Delay task. During the threat-reward condition (shown here), a visual cue stimulus (diamond-shape overlaid with dollar sign) signaled that participants could win extra monetary reward if they respond accurately before the target display disappears and also a mild electric shock could occur at the onset of the target display (independent of the performance). Participants were instructed about the meaning of the cue stimuli prior to task execution. During the target phase, participants were asked to indicate whether the shape was a circle or a square. Following the target phase, participants received feedback about the monetary reward (B) Six different types of visual cues at the start of each trial informed participants about the motivation and threatening circumstances.

One second after target onset, participants received visual feedback (1 s) indicating their performance and monetary reward or punishment, as well as their cumulative earnings until that moment in time. During reward trials, participants won 20 cents per trial if they responded correctly before the target disappeared. The reward was indicated by presenting "+$0.2". When they failed to get rewarded, "+$0.0" was displayed. During punishment trials, they lost 10 cents per trial if the response was incorrect or made after target was disappeared from display. When they successfully avoided the punishment, "-$0.0" was presented. Otherwise, "-$0.1" was displayed on the screen. During control trials (no reward and no

punishment), participants earned zero cents irrespective of their performance. Absolute value of punishment was half of the reward. I chose the asymmetric values based on the argument that the sensitivity to losses is higher than gains (e.g., Tversky & Kahneman, 1992). On average participants earned $22 (beyond their base pay). During fast and correct trials across all conditions, visual feedback containing the words “Correct” was displayed with monetary reward/punishment. During incorrect or slow-correct trials across all conditions, visual feedback containing the words “Wrong” or “Too Slow”, respectively, was shown. Finally, a 1-5 s variable inter-trial interval (ITI) was given after offset of the visual feedback.

A practice run was performed during the anatomical scan. The experimental procedure was identical to the “main runs” with the following exceptions. No physical shock was administered; participants were informed that they were not accumulating reward/punishment during practice even though they received feedback about monetary incentives; target faces displayed during practice run were not repeated during “main runs”.

For the presentation of visual stimuli and recording of participant’s responses, Presentation software (Neurobehavioral Systems, Albany, CA, USA) was used. Behavioral responses were collected using an MRI-compatible response box. Skin conductance response (SCR) data were also collected using the MP-150 system (BIOPAC Systems, Inc., CA, USA) with a 0.05 Hz high-pass hardware filter at a sampling rate of 250 Hz by using MRI-compatible electrodes attached to the index and middle fingers of the left hand.

Each participant performed 9 “runs” of the main task (two participants had 7 and 8 runs, respectively). Each run consisted of 48 trials, resulting in a total of 432 trials. All possible combinations of trial types were intermixed randomly but with the constraint that that each

possible trial combination occurred an equal number of times in terms of the stress, motivation, and facial expression. Gender of the face stimulus was also counterbalanced across trial types. To keep the trial types balanced after exclusion of the actual physical-shock trials (see *Behavioral data analysis* below), the subsequent trial type after the physical-shock trial always belonged to the safe condition.

MR data acquisition

MR data were collected using a 3 Tesla Siemens TRIO scanner (Siemens Medical Systems, Erlangen, Germany) with a 32-channel head coil (without parallel imaging). Each scanning session began with a high-resolution MPRAGE anatomical scan (TR = 1900 ms, TE = 4.15 ms, TI = 1100 ms, 1 mm isotropic voxels, 256 mm field of view). Subsequently, for each functional run, 184 EPI volumes were acquired with a TR of 2500 and TE of 25 ms. Each volume consisted of 44 oblique slices with a thickness of 3 mm and an in-plane resolution of 3 X 3 mm (192 mm field of view). Slices were positioned approximately 30 degrees relative to the plane defined by the line connecting the anterior and posterior commissures, helping to decrease susceptibility artifacts at regions such as the orbitofrontal cortex and amygdala.

General fMRI data analysis

Pre-processing of the data was done using tools from the AFNI software package (Cox, 1996; http://afni.nimh.nih.gov/afni). The first 3 volumes of each functional run were discarded to account for equilibration effects. The remaining volumes were slice-time corrected using Fourier

interpolation such that all slices were realigned to the first slice to account for the timing offset between slices. Six-parameter rigid-body motion correction within and across runs was performed using Fourier interpolation (Cox and Jesmanowicz, 1999) such that all volumes were spatially registered to the first volume. To normalize the functional data to Talairach space (Talairach and Tournoux, 1988), initially each subject's high-resolution MRPAGE anatomical volume was spatially registered to the so-called TT_N27 template (in Talairach space) using a 12-parameter affine transformation; the same transformation was then applied to the functional data. All volumes were spatially smoothed using a Gaussian filter with a full-width at half maximum of 6 mm (i.e., two times the voxel dimension). Finally, the signal intensity of each voxel was scaled to a mean of 100.

Voxelwise analysis

Each participant's fMRI data were analyzed using multiple linear regression with AFNI. There were six trial types for cue phase and 12 trial types for target phase. However, as hemodynamic responses may contain sustained responses during the anticipation of shock and reward/punishment, as well as transient responses for cue stimulus processing, two separate regressors were used for each event type during cue phase (Fig. 11): one is for modeling transient responses with a standard hemodynamic response function (Cohen, 1997), and the other is for modeling sustained responses with a duration-modulated boxcar function individually for each trial (function "dmBLOCK5" with "IM" option in AFNI; for related approaches, please see, Grupe et al., 2012). As an index of the sustained responses, I averaged the estimated responses of individual trials for each trial types, separately.

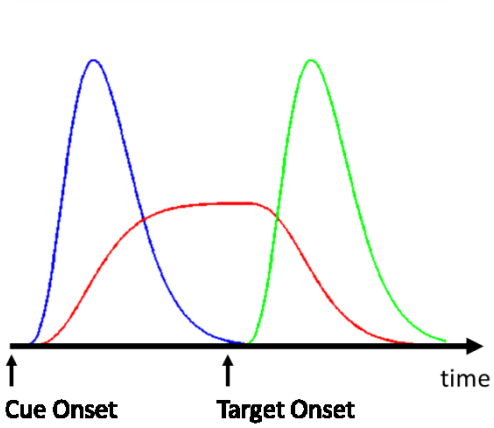

Figure 11. Modeling of the BOLD signal during a trial. Hemodynamic responses to cue stimulus may contain transient response for stimulus-related processing and sustained response for anticipatory processing before target presentation. For a single trial, three distinct regressors were used: cue-transient response (blue line), cue-sustained response (red line), and target responses (green line). Amplitude of responses and interval between cue and target onset are selected arbitrarily for visualization.

There were a total of 24 main event types in the design matrix: during the cue phase, safe and threat events, separately for the control (no-reward and no-punishment), reward, and punishment conditions. The event types for cue phase separated into two phases, again: cue-transient and -sustained. During the target phase, neutral and fearful face, separately for event types of cue phase. Threat trials that involved physical shock, subsequent safe trials, as well as error and RT outlier trials (see, *Behavioral data analysis*) were modeled separately using additional regressors of no interest (separately for the cue and target phases). Constant, linear, and quadratic terms were included for each run separately (as covariates of no interest) to model baseline and drifts of the MR signal. For the target phase data, because responses were expected to be transient and essentially canonical, all regressors were convolved with a standard hemodynamic response function (Cohen, 1997). Accordingly, response strength was indexed in the standard way (i.e., by estimating a single regression coefficient per condition).

Event-related designs allow the estimation of different event types when they occur in a randomized fashion. However, the present study, by design, required a fixed order between the cue and target phases. Thus, I randomized the delay between cue and target phases as well

as the inter-trial interval (for a similar strategy, see Padmala & Pessoa, 2011; Choi et al., 2012). In this manner, correlations and variance inflation factor between different regressors for cue-delay responses were lower than 0.33 and 3.26, respectively. It allowed me to estimate responses during the cue-delay phase separately from cue-transient and target phases.

Group analysis

Whole-brain voxelwise random-effects analyses were restricted to gray-matter voxels based on the FSL automated segmentation tool [“FAST” (FMRIB's Automated Segmentation Tool)] (http://www.fmrib.ox.ac.uk/fsl/). The main goal of this study is to investigate how the motivational processing of reward and punishment would be modulated by threat of shock during anticipation/delay phase. Thus, I initially conducted a repeated-measure ANOVA with *Motivation* (control, reward, punishment; safe and threat conditions were pooled) based on delay phase response. The alpha-level for voxelwise statistical analysis was determined by simulations using the 3dClustSim program of the AFNI toolkit. For these simulations, the smoothness of the data in three directions was estimated using 3dFWHMx on the residual time series of graymatter voxels in each participant and then averaged across participants (FWHMx = 7.61 mm; FWHMy = 7.48 mm; FWHMz = 7.03 mm). Based on a voxel-level uncorrected alpha of .005, simulations indicated a minimum cluster extent of 32 voxels for cluster-level corrected alpha of .05.

Regions of interest (ROI) analysis

In order to investigate the response patterns of the loci showing significant *Motivation* effect during the delay phase, I carried out an ROI analysis. For each participant, ROIs were defined in an independent fashion by using a leave-one-subject-out method. For each subject, I first created 5-mm radius spherical ROIs centered at the peak voxel of cluster showing the significant *Motivation* effect based on data from all subjects, except that subject. Then, for each of the six main conditions of interest, delay-phase responses of voxels that showed the significant *Motivation* effect in the "left-out" participants were averaged within the participant's ROI. I repeated this procedure for each subject and thus was able to conduct subsequent analyses for each ROI defined in a non-biased fashion. Using the ROI data, two separate two-way ANOVAs were conducted, in which motivation-related conditions (control, reward, punishment) were broken down into two factors, *Reward* (control, reward) and *Punishment* (control, punishment). Then, I ran 2 *Threat* (safe, threat) x 2 *Reward* (control, reward) repeated-measure ANOVA and 2 *Threat* (safe, threat) x 2 *Punishment* (control, punishment) repeated-measure ANOVA.

Skin conductance responses (SCRs)

Each participant's SCR data were initially smoothed with a median-filter over 50 samples (200 ms) to reduce scanner-induced noise and resampled at 1 Hz. The pre-processed SCR data were analyzed using multiple linear regression by using the AFNI software package (Cox, 1996; http://afni.nimh.nih.gov/afni) in the same way as fMRI data; for related approaches, please see Bach, Flandin, Frinston, and Dolan (2009) and Choi et al., (2012). There were six trial types for cue phase and 12 trial types for target phase. There were a total of 18 main event types in the

design matrix. Trials that involved physical shock, subsequent safe trials, as well as error and RT outlier trials were modeled using three additional regressors of no interest. No assumptions were made about the shape of the SCR function. Average response to each trial type was estimated via deconvolution. Responses were estimated starting from event onset to 15 s post onset using cubic spline basis functions. This method is closely related to the use of finite impulses ("stick functions"), the commonly employed technique that can be considered the simplest form of basis expansion. Cubic splines allow for a smoother approximation of the underlying responses, instead of the discrete approximation obtained by finite impulses. Constant, linear, and quadratic terms were included for each run separately (as covariates of no interest) to model baseline and drifts of the SCR. As an index of response strength, for each event type, I used the peak estimated response between 5–6 s after stimulus onset (as determined via the spline-based estimates). In order to equalize variance, response-strength indices were transformed by using a logarithm function [$\log_{10}$(1+SCR)]. As in the ROI analysis, two separate two-way ANOVAs were conducted on the log-transformed SCRs: 2 *Threat* (safe, threat) x 2 *Reward* (control, reward), and 2 *Threat* (safe, threat) x 2 *Punishment* (control, punishment). The alpha-level was .05.

Behavioral data analysis

Trials during which actual shocks were delivered and the subsequent (safe) trials were discarded, thus leaving 24 trials per trial type. Trials with response time (RT) exceeding three standard deviations from the condition-specific mean were discarded from further analysis (0.36 %) as outliers. Trials in which participants made incorrect responses (9.40%) were also excluded from further behavioral analyses, but "slow" trials during which a correct response was made after

the target disappeared were included. For each participant, mean RT data were determined as a function of *Threat* (safe, threat), *Motivation* (control, reward, punishment), and *Face* (fearful, neutral). Additionally, two separate two-way ANOVAs were conducted on the mean RT data: 2 *Threat* (safe, threat) x 2 *Reward* (control, reward), and 2 *Threat* (safe, threat) x 2 *Punishment* (control, punishment). The alpha-level was .05.

Results

Skin Conductance Responses

The main purpose of current study was to investigate how punishment processing is influenced by threat compared to how reward is influenced by threat. Accordingly, two separate ANOVAs were conducted (Fig.12A): *Threat* (safe, threat) x *Reward* (control, reward) and *Threat* (safe, threat) x *Punishment* (control, punishment). In the analysis of *Threat* (safe, threat) X *Reward* (control, reward), a main effect of *Threat* showed a trend to significance ($F_{1, 24}$ = 4.01, p = .057), indicating greater SCRs in threat condition than safe. Main effect of *Reward* and interaction effect of with *Threat* were not observed (Fs < 0.26). In the analysis of *Threat* (safe, threat) X *Punishment* (control, punishment), a main effect of *Threat* did not reach significance ($F_{1, 24}$ = 2.68, p = .115). A main effect of Punishment and the interaction effect with *Threat* were not detected (Fs$_{1, 24}$ < 2.44).

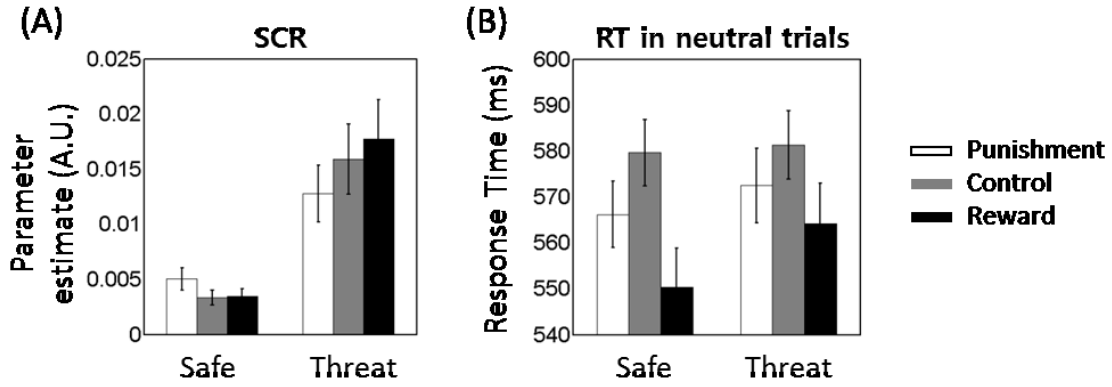

Figure 12. SCR and behavioral results. (A) SCR data during delay phase revealed significant main effect of *Threat*, but not interaction effect with reward or punishment. (B) Reaction time data during neutral trials revealed that threat showed marginally significant interaction with reward, but interaction effect with punishment did not reach to significance. Error bars in all panels denote the standard error of mean. A.U., arbitrary units.

Behavioral results

Reaction time data were evaluated according to a 2 *Threat* (safe, threat) x 3 *Motivation* (control, reward, punishment) x 2 *Face* (neutral, fearful) repeated–measures ANOVA. A significant main effect of *Motivation* was detected ($F_{2, 48}$ = 29.72, p < .001). Participants showed faster RT in reward (549 ms) condition than punishment (562 ms; t_{24} = 4.17, p < .001) and control (572 ms; t_{24} = 6.75, p < .001) conditions. Mean RTs were also faster in punishment than control (t_{24} = 4.29, p < .001). The main effect of *Threat* was not significant ($F_{1, 24}$ = 0.74), and interaction between *Threat* X *Motivation* showed a trend to significance ($F_{1, 24}$ = 2.43, p = .099). The 3rd factor, *Face*, showed a main effect ($F_{1, 24}$ = 2.43, p = .099), and interaction effect with *Threat* ($F_{1, 24}$ = 8.57, p = .007), but not with *Motivation* ($F_{2,48}$ = 0.31). Finally, a 3-way interaction was detected ($F_{2, 48}$ = 4.11, p = .023).

The 3-way interaction implies that the impact of threat and reward/punishment on behavior would be dependent on the affective property of target stimulus such as fearful face

(Robinson et al., 2012). In order to exclude the influence of face expression on performance, I ran the subsequent analyses only during "neutral" face trials (Fig.12B). It allowed me to compare the behavioral data with imaging data during the cue-delay phase. In addition, the main purpose of current study is to investigate how punishment processing is influenced by threat compared to interaction between threat and reward. Thus, like in SCRs data, the *Motivation* factor was broken down into two parts, *Reward* (control, reward) and *Punishment* (control, punishment), and two separate ANOVAs were conducted, *Threat* (safe, threat) x *Reward* (control, reward) and *Threat* (safe, threat) x *Punishment* (control, punishment).

In the analysis of *Threat* (safe, threat) X *Reward* (control, reward), a main effect of *Threat* showed a trend to significance ($F_{1, 24}$ = 4.23, p = .051). Mean RTs in threat condition (573 ms) was slower than safe (565 ms). A significant main effect of Motivation was detected ($F_{1, 24}$ = 25.21, p <.001). Mean RTs in reward condition (557 ms) was faster than control (581 ms). Of interest, a moderate interaction effect was detected ($F_{1, 24}$ = 3.86, p = .061). To investigate the source of the interaction effect, t-tests were conducted. Mean RTs during safe-reward trials (550 ms) were shorter than threat-reward trials (564 ms; t_{24} = 2.61, p = .015). There was no difference between safe-control (580 ms) and threat-control conditions (581 ms; t_{24} = 0.38). The analysis of *Threat* (safe, threat) X *Punishment* (control, punishment) also showed a main effect of *Punishment* ($F_{1, 24}$ = 9.54, p = .005). Mean RTs in punishment condition (569 ms) were faster than control (581 ms). However, a main effect of Threat and the interaction effect with *Punishment* did not reach to significance (Fs$_{1, 24}$ < 1.22).

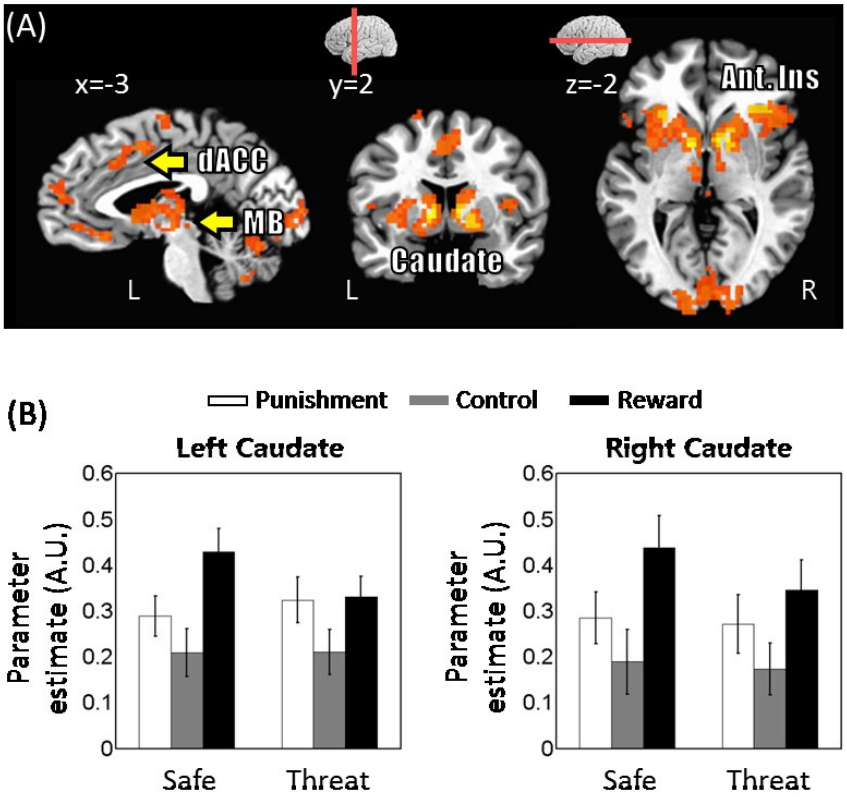

Figure 13. Cue-delay phase responses. (A) Voxels that showed significant main effect of *Motivation* (displayed at $p < 0.05$, cluster-level corrected). MB, midbrain; dACC, dorsal anterior cingulate cortex; Ant. Ins, anterior insula (B) Mean estimated hemodynamic responses from left and right ventral caudates. Error bars in bar plots denote the standard error of mean.

Functional MRI results

In voxelwise analysis, a significant *Motivation* effect was observed in several structures including bilateral striatum (peaked at ventral caudate), bilateral anterior insula, and dorsal ACC (Fig. 13, Table 5). I selected bilaterally caudate, anterior insula, frontal eye field (FEF), midbrain/VTA, and dorsal ACC for ROI analyses. Previous studies showed that midbrain structures were recruited during aversive processing as well as appetitive processing (Matsumoto & Hikosaka, 2009; Carter, et al., 2009). The caudate is also engaged during both reward and punishment anticipation (Carter et al., 2009; Wu et al., 2014) as well as electric shock (Choi et al., 2012;

Jensen et al., 2003). The anterior insula was indicated to process aversive events (Paulus & Stein, 2006). However, it also responds to cue stimulus signaling monetary gains (Liu, et al., 2011; Padmala and Pessoa, 2011) and monetary losses (Knutson and Greer, 2008). Finally, the dorsal ACC was suggested to function in "adaptive control" (Rushworth & Behrens, 2008; Shackman et al., 2011). However, it also participates in processing of reward (Bush et al., 2002; Shidara & Richmond, 2002; Shima & Tanji, 1998) and loss aversion (Fujiwara et al., 2009; Kuhnen and Knutson, 2005).

Left caudate. In the analysis of *Threat* (safe, threat) X *Reward* (control, reward), a main effect of *Threat* showed a trend to significance ($F_{1, 24}$ = 4.20, p = .051), indicating responses in the left caudate was greater during safe. A significant main effect of *Reward* was detected ($F_{1, 24}$ = 34.39, p <.001), showing greater responses during reward than control. Of interest, the reward effect was modulated by threat ($F_{1, 24}$ = 5.68, p = .025). To investigate the source of the interaction effect, t-tests were conducted. Responses during safe-reward trials were shorter than threat-reward trials (t_{24} = 3.83, p < .001). There was no difference between safe-control and threat-control conditions (t_{24} = 0.06). In the analysis of *Threat* (safe, threat) X *Punishment* (control, punishment), a significant main effect of *Punishment* was observed ($F_{1, 24}$ = 12.91, p = .002). Responses during punishment were greater than control condition. However, main effect of *Threat* and the interaction effect with *Punishment* did not reach to significance ($Fs_{1, 24}$ < 0.68).

Right caudate. In the analysis of *Threat* (safe, threat) X *Reward* (control, reward), a main effect of *Threat* showed a trend to significance ($F_{1, 24}$ = 2.82, p = .106), indicating responses were

greater during safe. A significant main effect of *Reward* was detected ($F_{1, 24}$ = 34.39, p <.001), showing greater responses during reward than control. The interaction between *Threat* and *Reward* did not reach to significance ($F_{1, 24}$ = 2.03, p = .167). However, the t-tests revealed that responses during safe-reward trials were greater than the responses during threat-reward trials (t_{24} = 2.60, p = .016) whereas there was no difference between safe-control and threat-control conditions (t_{24} = 0.32). In the analysis of *Threat* (safe, threat) X *Punishment* (control, punishment), a significant main effect of *Punishment* was observed ($F_{1, 24}$ = 9.18, p = .006). Responses during punishment were greater than control condition. However, main effect of *Threat* and the interaction effect with *Punishment* did not reach to significance (Fs$_{1, 24}$ < 0.26).

Other brain regions. The repeated-measures ANOVAs of *Threat* X *Reward* and *Threat* X *Punishment* were conducted using ROI data from bilateral anterior insula, midbrain, and dorsal ACC. However, none of those regions showed a main effect of *Threat* and interactions of *Threat* X *Reward* and *Threat* X *Punishment* (Fs < 2.28).

Discussion

In the current experiment, two competing hypothesis were tested to investigate how threat interaction with reward and punishment. According to the “resource hypothesis”, task-irrelevant threat recruits attentional resources that are also used by goal-directed processing for winning reward and avoiding punishment. Thus, both reward and punishment processing would be reduced by threat. Alternatively, the “valence hypothesis” predicts that processing aversive

stimuli opposes processing appetitive stimuli. Thus, threat would not interact with punishment processing but it would interact with reward processing.

To investigate how reward and punishment processing is modulated by threat of shock, I used a task with motivational cues signaling the chance of monetary reward or punishment, and a threat cue signaling a chance of mild aversive shock. The experimental design used here allowed me to measure responses during the preparatory/anticipatory delay phase to probe the impact of threatening stimuli on motivational processes independent of stimulus processing. In behavioral data, it was observed that both of reward and punishment have beneficial effects on behavior (i.e., faster face discrimination responses). However, threat counteracted the reward effect but not the punishment effect. SCR data revealed greater responses during threat than safe. In imaging data, a main effect of *Motivation* was observed in various regions related to reward processing. Particularly, the bilateral caudate, anterior insula, midbrain, and dorsal ACC were engaged to motivational context more strongly (reward, punishment > control condition) regardless of its motivational valence, parallel with previous studies (e.g. Carter et al., 2009). Importantly, in left caudate, the impact of anxiety/stress on motivational processing was observed only in appetitive (reward anticipation), but not in aversive circumstances (punishment anticipation). In right caudate, the interaction effect of threat with reward as well as punishment was not observed. However, direct comparison of reward trials in safe and threat conditions showed that responses to reward were smaller in threat than safe. Overall, the findings suggest that threat has specific effects on appetitive motivation but not on aversive motivation.

Ventral striatum, including nucleus accumbens and caudate, have been indicated as one of the main regions related to reward and punishment processing (Carter et al., 2009; Cooper

and Knutson, 2008; Wu et al., 2014). Some human imaging studies reported that the neural substrates in the ventral striatum were altered depending on the valence of the reinforcement (reward or punishment) in terms of the activation level (Tom et al, 2007) or location (Seymour et al, 2007). Recently, Bissonette et al., (2013) demonstrated that different populations of neurons in ventral striatum participate in reward and punishment anticipation. The results in current study revealed that caudate is responsible for punishment processing as well as reward, but its engagement level in motivational processing can be modulated by aversive processing.

Anterior insula and dorsal ACC are involved in threat- and reward-processing (Banks et al., 2007; Everitt et al., 2003; Fujiwara et al., 2009; Kalin et al., 2005; Knutson et al., 2005;Liu et al., 2011; Mizuhiki et al., 2012; Mobbs et al., 2010), and interconnected with striatum (Haber and Knutson, 2010). In the previous experiment in Chapter 2, I observed an interaction between threat and reward in both of anterior insula and dorsal ACC. However, this interaction was not replicated in the current experiment, in which two motivational conditions were used (reward and punishment). Also, the main effect of *Threat* was not observed in those regions even though behavioral and SCR data showed the main effect of *Threat*. The weak effect of threat was somewhat unexpected given the previous results in Chapter 2. One possibility is that, additional trial type (punishment) was included in current experimental design compared with the previous experiment while the degree of freedom of the error term (number of subjects) was similar to the previous study. It might lead to larger error term size, resulting in weak detecting power of the interaction effect. Similarly, participants experienced motivating situation (reward or punishment condition) twice as often as the non-motivational situation (control condition). Perhaps, the overall motivation level during the current experiment was higher than the previous experiment which had only reward trials. The relatively heightened motivation level

might reduce the impact of threat, reducing the power to detect interactions between threat and reward.

In the safe condition, responses to punishment were smaller than reward. One possibility is that absolute magnitude of monetary punishment was half of the reward. We selected the ratio of punishment value to reward to balance motivation level between reward and punishment, based on previous studies (Engelmann and Pessoa, 2007; Tom et al., 2007) because it was suggested that sensitivity to loss is higher than gain (Tversky & Kahneman, 1992). Even though the impact of punishment was less than reward in the current study, the additive effect of threat on punishment is still supportive to "valence hypothesis" because the punishment effect was not reduced under threat of shock. Another possibility is that, in reward and punishment conditions, participants were instructed to discriminate target face as fast and accurately as possible to win and avoid losing monetary incentives. For successful avoidance of punishment, participants were forced to engage on the target stimulus. If the "task engagement" led to tendency of approaching behavior, it would conflict with the property of punishment whereas it is compatible with property of reward (Hardin et al., 2006).

Competition and integration

In current study, interaction effect between threat and reward was observed. Specifically, responses in caudate during safe-reward trials were reduced compared to the responses during threat-reward trials. In contrast, in same site, responses to punishment were not influenced by threat of shock (Fig. 13). If threat processing competed with reward/punishment processing for attentional/effortful resources, responses to punishment would be reduced like responses to

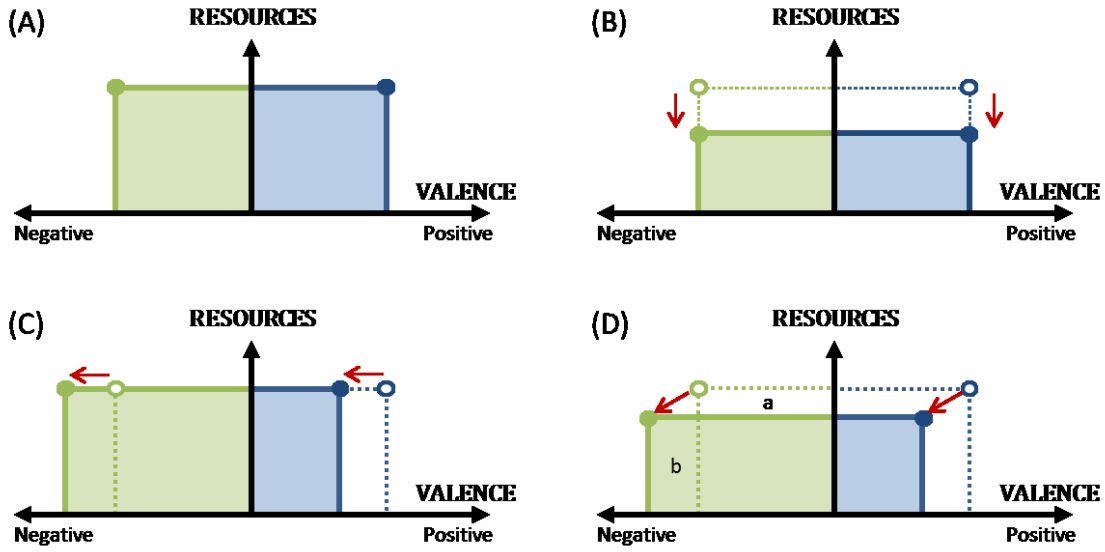

Figure 14. Effect of threat on processing resources and/or valence. Green squares represent responses to punishment. Blue squares represent responses to reward. Red arrows represent effect of threat. (A) Responses to reward and punishment in safe condition. (B) If threat affects processing resources, responses to both reward and punishment will be decreased. (C) If threat affects valence, responses to reward will be decreased whereas responses to punishment will be increased. (D) If threat affects both resources and valence, responses to reward will be decreased. However, change of responses to punishment will be minimal if areas of *a* and *b* are similar with each other.

reward (Fig.14B). However, analysis of behavioral and imaging data did not showed the decreased responses to punishment in threat condition. Therefore, it is more plausible that impact of threat modulates motivational valence of reward and punishment rather than processing resources.

How does the threat of shock influence the motivational valence of reward and punishment? One possible way is that individual valence of threat and reward/punishment would be integrated into an overall valence. For instance, when both monetary reward (positive) and electric shock (negative) is anticipated, an overall valence will be smaller than reward-only condition. Thus, responses to reward will be weaker under threat of shock than safe (Fig.14C). Some human decision-making studies provided supporting evidence that reward valuation was

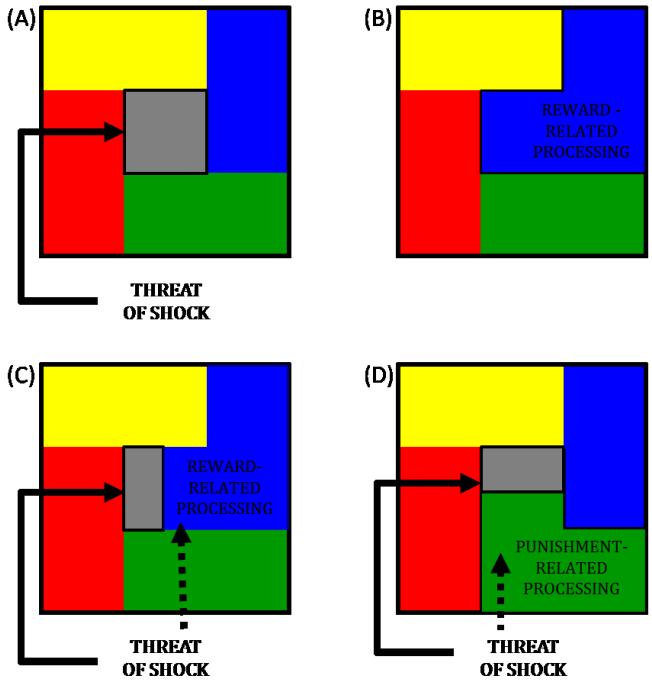

Figure 15. Effect of threat on executive functions. (A) Threat of shock will recruit attentional/effortful resources that are shared with other executive functions. Individual component of executive functions are represented by color squares. (B) Processing to achieve goal (reward) would be improved by sharpening the processing (represented by outline of blue square), and utilizing the "common resources". (C) The impact of reward on executive function will be reduced by threat in two ways: occupying "common resources" (arrow with solid line) and blunting the goad-directed processing (arrow with dashed line). (D) During punishment processing, threat will use the processing resources (arrow with solid lie). At the same time, threat will amplify negative valence of punishment (arrow with dashed line). Consequently, the impaired processing due to lack of resources will be compensated.

reduced when physical pain is accompanied by the rewarding outcome (e.g. Park et al., 2011; Talmi, et al.). On the contrary, when both threat and punishment is anticipated, an overall negative valence will be greater than punishment-only condition. Recently, Robinson et al (2011, 2012) showed that responses to fearful face (vs. happy face) were enhanced under threat of shock. The results suggest that aversive processing (fearful face or punishment anticipation) can be amplified under aversive circumstances (threat of shock).

However, it does not completely rule out the possibility that threat functioned as a "distractor". If threat affected motivational valence without influencing processing resources, responses to punishment should be increased as a function of negative valence when electric shock was anticipated (Fig.14C). However, I could not found the evidence showing that responses to punishment change depending on threat. It suggests that threat might affect both of attentional resources and motivational valence: decrease of available resources for goal-directed processing and increase of negative valence (Fig.14D).

According dual-competition model (Pessoa, 2009), processing of emotional stimuli demand attentional/effortful resources which are required for other executive functions. If the resources are utilized in processing of task-irrelevant emotional stimulus (e.g. electric shock), cognitive processing for task performance is impaired (Fig.15A). However, if reward is anticipated, executive functions will be enhanced. In dual-competition model, two mechanisms of reward effect are hypothesized. One is that reward processing recruits processing resources from "common-pool". The other is that motivation to win reward sharpens the executive function related to goal achievement (Fig. 15B). Results in current experiment suggest that threat processing influences both effects of reward: the recruitment of attentional/effortful resources for reward processing can be distracted by threat (arrow with solid line in Fig.15C). In addition, the aversive valence of threat would reduce the appetitive valence of reward, thus improvement of executive function by reward would be relatively blunted (arrow with dashed line in Fig.15C). When punishment is anticipated, executive functions will be enhanced like rewarding circumstances: recruitment of additional resources and improvement of goal-directed processing. If threat is anticipated in punishment circumstances, the "common resources" is still be utilized by threat processing (arrow with solid line in Fig.15D). However, the impact of threat

would enhance the punishment-related processing because punishment and threat have same "sign". Thus, the overall impact of threat on punishment would not be great.

Taken together, the present study partially supports the idea that threat processing influences anticipatory processing of appetitive outcome (reward), but not the anticipatory processing of aversive outcome (punishment). However, the results should be interpreted carefully because the previous results in Chapter 2 about the interaction between threat and reward were not fully replicated. The threat effect was relatively weak and the interaction effect between threat and reward was observed only in left caudate.

Table 5. Voxelwise analysis at delay phase (Peak talairach coordinates, $F_{2,48}$ values)

		Main effect of *Motivation*			
Peak Location		*x*	*y*	*z*	$F_{2,48}$
Occipital					
Middle occipital gyrus	L	-10	-97	2	15.01
	R	20	-88	5	13.27
Temporal					
Inferior temporal gyrus	L	-52	-49	-13	13.12
	R	44	-37	-22	10.07
Middle temporal gyrus	L	-46	-57	26	12.83
	R	59	-46	23	14.31
Frontal					
Frontal eye field	L	-19	-4	62	11.59
	R	29	-7	50	9.79
Supplementary motor area		2	-10	59	11.58
Anterior cingulate cortex		-4	20	35	8.85
Middle frontal gyrus	R	32	44	32	13.96
Superior frontal gyrus	L	-22	26	53	12.95
Ventro-medial prefrontal cortex		-4	26	-10	11.12
Rostral medial prefrontal cortex		-1	53	14	9.63
Anterior insula	L	-25	20	-1	24.46
	R	35	26	2	21.98
Subcortical					
Thalamus	L	-7	-13	2	12.92
	R	8	-19	14	16.91
Caudate	L	-7	2	2	26.18
	R	8	5	5	30.31
Cerebellum		2	-55	-16	11.49

CHAPTER 4: Concluding remarks

This dissertation investigated how reward and punishment processes are affected by anxiety/stress elicited by threat of electric shock. The first study used fMRI to examine the interaction between threat and reward processing to test two competing hypotheses. According to the "salience hypothesis", enhanced activation would be observed in the condition involving both reward and threat because of increased salience. However, according to the "competition hypothesis", reward and threat processing trade-off against each other leading to reduced activation in that condition. Analysis of skin conductance data during the delay phase revealed an interaction between reward and threat processing, such that the effect of reward was reduced during threat and the effect of threat was reduced during reward. Analysis of imaging data during the same task phase revealed competitive interactions between reward and threat processing in several regions, including the midbrain/VTA, caudate, putamen, BNST, anterior insula, middle frontal gyrus and dorsal anterior cingulate cortex. The interaction effect observed in multiple sites suggests competitive processes between threat and reward when they were processed simultaneously.

The competitive interaction between threat and reward can be interpreted in two ways. According to the dual-competition model (Pessoa, 2009), threat processing competes for attentional/effortful resources with other executive functions while reward improves processing efficacy possibly by reallocating available resources. The contrasting properties of threat and reward might have led the competitive interaction of them. Alternatively, competitive interaction between threat and reward might be due to valence of anticipated outcome. When both appetitive and aversive outcomes are expected (electric shock and monetary incentives), valence intensity of a stimulus might be reduced by another stimulus having opponent valence

(Konorski, 1967; Solomon & Corbit, 1974). However, the experimental design in previous study in Chapter 2 does not allow me to explain which mechanism was employed because electric shock and monetary reward had different properties along two dimension, valence and response-contingency. In previous experiment in Chapter 2, participants were informed about aversive and/or appetitive outcome on every trial. Aversive outcome was a mild electric shock which was occasionally administrated regardless of performance. Appetitive outcome was a visual feedback about monetary incentives depending on task performance.

One possible way to investigate the mechanism of the competitive processes would be to test interactions involving threat and punishment, because punishment is an aversive stimulus that also motivates behavior (Elliot&Covington, 2001; Guitart-Masip et al., 2012). Therefore, in the second fMRI study, I expanded the factorial design to include punishment in addition to threat and reward. By adding punishment condition, I could manipulate outcome valence (appetitive vs. aversive) while largely controlling motivational arousal. Two possible scenarios were tested: the “resource hypothesis” and the “valence hypothesis”. According to the “resource hypothesis”, reduced activation would be observed in the condition involving threat and punishment and the condition involving threat and reward because resources used by threat processing would reduce motivational impact of punishment and reward. The “valence hypothesis” also predicts reduced activation in the condition involving threat and reward because processing of aversive stimulus would oppose appetitive stimulus processing. However, the processing of punishment and threat would be additive because both stimuli are aversive. Analysis of behavioral data revealed that responses were facilitated in reward and punishment trials. The effect of reward interacted with threat as in the first experiment. However, the effect of punishment was not influenced by threat of shock. In parallel with behavioral data, imaging

data showed that the reward specific effect of threat was observed. Specifically, in caudate, responses during reward anticipation were reduced under threat of shock. However, responses to punishment were not influenced by threat.

Taken together, I investigated interactions between aversive and appetitive processing during anticipation of outcomes in normal healthy adult volunteers. In the first study, imaging data showed a trade-off pattern in regions such as midbrain, striatum, BNST, anterior insula, right MFG and dorsal ACC. In the second study, the competitive interaction between threat and reward was replicated in left caudate. However, in the same site, the interaction effect between threat and punishment was not observed. The findings from two studies suggest that aversive and appetitive processing counteract one another by reducing valance intensity of stimulus.

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