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### Paper:

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The Tipping Point: Value Differences and Parallel Dorsal-Ventral Frontal Circuits Gating  
Human Approach-Avoidance Behavior

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### Abstract

Excessive avoidance and diminished approach behavior are both prominent features of anxiety, trauma and stress related disorders. Yet our understanding of the brain mechanisms supporting gating of human approach-avoidance behavior is limited. Here, we used functional magnetic resonance imaging (fMRI) to track dorsal anterior cingulate and medial prefrontal (dACC/dmPFC) activation along an approach-avoidance continuum to assess sensitivity to competing appetitive and aversive contingencies and correspondence with behavior change. Behavioral and fMRI experiments were conducted using a novel approach-avoidance task where a monetary reward appeared in the presence of a conditioned stimulus (CS), or threat, that signaled increasing probability of unconditioned stimulus (US) delivery. Approach produced the reward or probabilistic US, while avoidance prevented US delivery, and across trials, reward remained fixed while the CS threat level varied unpredictably. Increasing the CS threat level (i.e., US probability) produced the desired approach-avoidance transition and inverted U-shaped changes in decision times, electrodermal activity and activation in pregenual ACC, dACC/dmPFC, striatum, anterior insula and inferior frontal regions. Conversely, U-shaped changes in activation were observed in dorsolateral and ventromedial prefrontal cortex and bimodal changes in the orbitofrontal and ventral hippocampus. These new results show parallel dorsal-ventral frontal circuits support gating of human approach-avoidance behavior where dACC/dmPFC signals inversely correlate with value differences between approach and avoidance contingencies while ventral frontal signals scale with the value of predictable outcomes. Our findings provide an important bridge between basic research on brain mechanisms of value-guided decision-making and value-focused clinical theories of anxiety and related interventions.

*Key words:* approach-avoidance; decision making; threat; conflict; anxiety; anterior cingulate.

## 1. Introduction

*"That's all I can stands, cuz I can't stands n'more!"*

Popeye: Lead character from the Thimble Theatre comic strip (1933)

Every individual has a tolerance level for environmental threat and aversive stimulation that aids self-preservation. As threat intensity escalates, a ‘tipping point’ is reached and we switch from engaging in reward-based approach to threat avoidance. Excessive avoidance accompanied by fear, anxiety and intolerance of threat are all core diagnostic features of anxiety, trauma and stress related disorders (Aldao et al., 2010; Craske et al., 2009; Dymond & Roche 2009; Grupe & Nitschke, 2013; American Psychiatric Association, 2013). Traditionally, neurophysiological research has focused on reward or threat processes independently, leaving open many questions regarding how reward-threat competition and conflict impact affective processes and behavioral adjustments (Mansouri et al., 2009; Hu et al., 2013). Fortunately, there is growing interest in how reward and threat systems maintain homeostasis, interact and modulate higher cognitive processes (Pochon et al., 2008; Pessoa, 2009; Talmi et al., 2009; Schlund et al., 2010; Aupperle et al., 2011; Spielberg et al., 2012; Bissonette et al., 2014; Hayes et al., 2014; Botvinick & Braver, 2015), as well as how impaired arbitration of reward and threat information may serve as a mechanism for observed decreases in approach behavior in depression and increases in avoidance behavior in anxiety (Stein & Paulus, 2009; Aupperle & Martin, 2010; Trew, 2011; Dillon et al., 2014). The purpose of this investigation was therefore to address several gaps in our understanding of the underlying brain mechanisms supporting transitions between approach and avoidance (AA) in response to escalating threat.

The AA distinction holds a prominent place in psychology and the utility of the distinction is evident across theoretical traditions, disciplines and content areas (Elliott, 2008). AA motivation is viewed as a basic process, with each component having a distinct energizing feature and direction, that

encompasses multiple dimensions, including arousal and valence (Lang, 1995), and operates across multiple levels, from rudimentary reflexes to cortical processes, in a hierarchical fashion (Elliott & Church, 1997). Within laboratory settings, AA motivation is operationalized in conflict paradigms via changes in the probability of responding towards appetitive stimuli, such as food, and away from aversive stimuli, such as shock (Millan, 2003; Pochon et al., 2008; Amemori & Graybiel, 2012; Aupperle et al., 2011, 2014; Sierra-Mercado et al., 2014; Löw et al., 2015). For example, in the Vogel Conflict Test water-deprived rats are offered a water bottle in which licks are accompanied by water and periodic punishing electric shocks (Vogel et al., 1971). Escalating shock intensity across trials/sessions increases the competition between the appetitive and aversive contingencies and gives rise to fear/anxiety along with a decline in approach behavior (Estes & Skinner, 1941). Moreover, there is a large literature showing benzodiazepine administration has anti-punishment effects that result in greater sustained approach responding (Lippa et al., 1978; Kilts et al., 1981; Herberg & Williams, 1983; Liljequist & Engel, 1984; Rowlett et al., 2006). Generally, AA conflict situations like this create a differential or contrast between the values of choice options as defined by their contingencies, such that increasing threat value eventually surpasses reward value resulting in an AA transition. Botvinick (2007) has proposed that such conflict is costly, demanding and inherently aversive, much like other aversive events, such as monetary loss and pain. In addition, the aversive properties of demand produced through conflict have been proposed to serve as a learning signal that drives avoidance (Kool et al., 2011), underscoring both negative affective responses and avoidance as key elements of conflict created when appetitive and aversive contingencies compete.

The dorsal anterior cingulate (dACC) and dorsomedial prefrontal cortex (dmPFC) are regions implicated in AA, decision making and valuation, and may play a central role in optimizing AA behavior (Pochon et al., 2008; Amemori & Graybiel, 2012; Spielberg et al., 2012; Grupe & Nitschke,

2013; Shenhav et al., 2013; Cavanagh & Shackman, 2015). Recently, Aupperle et al. (2014) gave participants mixed choices with varying levels of conflict produced by manipulating probabilities of positive and negative outcomes. Imaging analyses comparing trials with conflict to trials with no conflict (an average of reward-only and threat-only trials) showed greater activation in bilateral dACC as well as in the anterior insula, striatum (e.g.) and right dorsolateral prefrontal cortex (see also, Pochon et al., 2008; Friedman et al., 2015). Other investigations also suggest involvement of the orbitofrontal cortex (Mansouri et al., 2014) and hippocampus in AA (Bannerman et al., 2003, 2004; Kumaran & Maguire, 2006, 2007; Bach et al., 2014; Bannerman et al., 2014; Oehrman et al., 2015). Recently, Bach et al., (2014) developed a novel AA conflict task modeled after a predation scenario that required subjects to actively pursue available rewards in the presence of predator displaying varying levels of threat. Increased threat was associated with increased passive avoidance and behavioral inhibition and activation in anterior hippocampus as well as right inferior frontal gyrus/insula, bilateral parahippocampal gyrus, and right fusiform gyrus. Moreover, patients with hippocampal lesions showed reduced passive avoidance across all threat levels.

Strict response conflict based interpretations of ACC activation have been challenged by evidence showing activation to cue information under conditions without choice or response competition (Croxson et al., 2009; Choi et al., 2013; Hu et al., 2013). For example, Pochon et al. (2008) separated decision and response phases and found activation was isolated to the decision phase on trials not requiring a response, concluding that activation reflected decision conflict and not response output or conflict. ACC lesions have also been shown to disrupt optimal choice behavior by producing a deficit in the ability to benefit from reinforcement history and integrate risk and payoff, underscoring a potential role in learning the value of actions rather than conflict monitoring or error detection (Kennerly et al., 2006). Other accounts suggest ACC activation during cost-benefit decision-making reflects integration

of values across different stimuli (Talmi et al. 2009; Park et al., 2011) as well as regulating negative emotional valence (Amemori & Graybiel, 2012).

The contributions of dACC and dmPFC in supporting AA transitions are further suggested by neuroimaging findings employing paradigms based on simulated foraging. In the modal foraging task, it is thought that decisions involve comparing the value associated with staying in a rewarding patch with a diminishing return (choice A) to the value associated with switching to a new patch (choice B), which is often a ‘risky’ alternative in that it offers a larger but less probable reward. At some point, the value of the alternative path exceeds the value of the current patch or default choice prompting a switch (i.e., transition). Foraging switches that occur when the reward value exceeds remaining in a patch are analogous to AA transitions that occur when a current threat (or estimate of predator risk) exceeds the value associated with approach for reward. It is known that ACC activity increases with the probability of switching to the new patch implying that activity tracks with the value of the alternative or foraging option (Hayden et al., 2011; Kolling et al., 2012, 2014; Mobbs et al., 2013). These different perspectives are highlighted in Figure 1A, which shows hypothetical changes in activation along the approach-avoidance continuum associated with conflict, integration/comparison and foraging views, with the latter emphasizing monotonic increases in activation. Challenges to the foraging view have come from expanded foraging conditions that give greater consideration to behavioral changes. Recent findings reveal that ACC activation increases up to a switch point and then declines, consistent with a negative quadratic change (Figure 1A), and suggests activation tracks with changes in choice difficulty rather than continues to increase with the value of an alternative choice (Shenhav et al., 2014).

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Insert Figure 1 here

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While the evidence supporting the *choice difficulty view* is convincing, questions remain about what variable(s) exhibit relative changes in the choice context in ways that give rise to ‘difficulty’. One explanation may be dACC/dmPFC generates an inverse ‘*value difference*’ signal that increases as the difference between the values of choice options decreases (Basten et al., 2010; Philiastides et al., 2010; Hare et al., 2011; Rushworth et al., 2012) (Figure 1A), with the result that choice is more difficult and time consuming. Regional changes in activity along the AA continuum may therefore reflect arbitration of relative value differences between choice options as defined by the appetitive and aversive contingencies. Ventral frontal regions supporting valuation processes may also work in parallel with dACC and dmPFC regions (Wallis & Kennerley, 2011). However, ventral regions may exhibit a ‘*value difference*’ signal that increases as the difference between values of choice options increases (Rushworth et al., 2012) (Figure 1A). It is notable that increases in the difference between values would also coincide with an increase in outcome predictability in the choice context. Changes in ventral frontal activity along the AA continuum may therefore be tied to changes in the value of the immediate choice established by the predictability of the choice outcome.

The present investigation evaluated these hypotheses in one behavioral and one functional magnetic resonance imaging (fMRI) experiment using different participant groups. Participants first underwent threat conditioning where they learned higher vertical levels on a ‘threat meter’ (conditioned stimulus (CS) threat level) signaled greater probabilities of aversive unconditioned stimulus (US) delivery. Next, participants completed an AA task modeled after those used in prior studies on AA (Amemori & Graybiel, 2012; Aupperle et al., 2014; Sierra-Mercado et al., 2014). In our AA task, a fixed monetary reward was presented in the presence of a CS threat level, which was varied across trials. Approach choices produced the reward or the probabilistic US while avoidant choices reduced the threat level and prevented US delivery. Increasing CS threat level relative to the fixed reward enabled us to



parametrically manipulate ‘value differences’ between approach for reward and threat avoidance. Value differences between AA choice options were greatest at low and high CS threat levels (i.e., most different), but less at mid-range CS threat levels (most similar). As shown in Figure 1B, if dACC/dmPFC responses vary *inversely* with value differences then activation associated with CS threat increases should show a negative quadratic change (an inverted U-shape function). Moreover, ventral frontal activation associated with CS threat increases should show a positive quadratic change (U-shape function), presumably reflecting changes in the value of the immediate choice established by outcome predictability. Finally, if dorsal and ventral regions work in parallel to gate AA behavior we would expect that near the AA transition dorsal regions would show the relatively greatest activation and ventral regions the relatively lowest activation.

## 2. Methods

Experiments 1 and 2 utilized different groups of participants. The methods used in both experiments were identical with the only exceptions being Experiment 1 measured skin conductance responses (SCR) during three sessions of the AA task while Experiment 2 measured brain activation with fMRI during two sessions of the AA task. In both experiments, a general set of instructions described the AA task for participants as making repeated decisions about whether to board spaceships they encounter (approach) or refuse to board spaceships (avoidance). To help decisions, an ‘alien threat meter’ was available that highlighted the chances a spaceship was laden with aliens that would sack their money and supplies. The task was to earn as much money as possible and prevent alien attacks.

### 2.1 Participants

In Experiment 1, nineteen right-handed adults ( $M_{\text{age}} = 22.8$ ,  $SD = 3.1$ , 11 males) participated. In Experiment 2, thirty right-handed adults ( $M_{\text{age}} = 24.1$ ,  $SD = 4.3$ , 16 males) participated. All participants reported being free of clinical disorders, metal in the body, and use of medications capable of altering central nervous system functioning and/or pregnancy. All provided written informed consent. Participants were compensated with a fixed amount for participation and earned additional money during the experimental task. The Institutional Review Boards for the Protection of Human Subjects at the University of North Texas and Texas Tech University approved this investigation.

## 2.2 Conditioned stimuli

Ten positions on a vertical bar served as ten distinct CSs (Figure 2A). Participants were told the “activated” level was highlighted with a ‘NOW’ prompt that appeared on a vertical bar (this was later described as a “threat meter”). The US was a compound aversive stimulus consisting of the simultaneous presentation of a \$1.00 loss prompt and 600 ms female scream (Delgado et al., 2006; Lau et al., 2008; Glenn et al., 2012; Schlund et al., 2015). Figure 2 shows the ‘threat meter’ levels were associated with nonlinear increases in the probability of US delivery. Levels 1-3 functioned as safe CS-s by virtue of not pairing them with US delivery (see below). In contrast, levels 4-10 served as ever more threatening CS+s by virtue of pairing them with increasing US probability (see Figure 2).

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 Insert Figure 2 here  
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## 2.3 Design

The procedure consisted of completing three consecutive steps: (a) *CS threat level pretesting* to ensure levels were viewed as neutral and responding was undifferentiated; (b) *Threat conditioning*,

which established different CS levels as threats through probabilistic US pairings; (c) *Approach-Avoidance acquisition* to facilitate learning approach at threat level 1 produced a monetary reward and avoidance at threat level 10 prevented US delivery. In Experiment 1, participants completed the AA task three times. In Experiment 2, neuroimaging occurred while participants completed the AA task twice during two consecutive scans.

#### 2.4 Behavioral data acquisition

Behavioral data consisted of condition-specific retrospective ratings of fear and US expectancy. After each condition, each CS threat level was individually displayed in a randomized order and ratings obtained in two different categories: Threat (“Please rate how much you felt threatened when the level was at <NOW>?”) measured using a 9-point scale (1=*None*, 5=*Moderate*, 9=*Severe*) and US expectancy (“If you chose money: please rate how much you would expect (likelihood) to lose money *if you did not choose to avoid* when the level was <NOW>?”) measured using a 9-point scale (1=*Never*, 5=*Uncertain*, 9=*Definite*). The AA task recorded the number of trials with an approach and avoidance response, decision (reaction) time (RT) and resulting outcome.

#### 2.5 SCR data acquisition

In Experiment 1, SCR were acquired with a sampling rate of 100Hz per second using SHIMMER™ (Burns et al., 2010) from two disposable Ag/AgCl electrodes (2 cm diameter) attached to the base of thenar and hyothenar eminence of the left hand.

#### 2.6 fMRI data acquisition

Neuroimaging data were collected in Experiment 2 during two consecutive fMRI scans sensitive to blood oxygen level dependent (BOLD) contrast with a 3T Siemens Magnetom Skyra equipped with a 20 channel head coil. T2\*-weighted echo-planar images consisted of 41 axial oriented slices with voxels measuring 3.5 x 3.45 x 3.5 mm (repetition time = 2000 ms, echo time = 20ms, 90 degree flip angle, field of view = 221 mm, 64 x 64 matrix, 278 volumes). To minimize equilibrium effects, the first four EPI volumes for each acquisition were discarded. Additionally a high-resolution T1-weighted image was obtained for anatomical reference (192 sagittal slices, voxels 0.9 x 0.9 x 0.9 mm, repetition time 1900 ms, echo time 2.49 ms, field of view = 240 mm).

## 2.7 Procedure

*2.7.1 CS threat level pretesting.* For Experiment 2, this step was completed before neuroimaging. Participants were presented with one trial of each CS level in a randomized order (Figure 2A). Each trial consisted of a 3 s CS presentation followed by a 5-7 s jittered ITI. Instructions emphasized paying attention to where the “NOW” cue appeared on the vertical bar. No US deliveries occurred. Afterwards, ratings of fear and US expectancy were obtained for each CS threat level.

*2.7.2 Threat conditioning/acquisition.* For Experiment 2, this step was completed before neuroimaging. A modified Pavlovian threat (fear) conditioning paradigm was utilized to establish different threat levels as CS+ and CS-, respectively. Figure 2A shows US probabilities associated with each CS level. Participants were given a stipend of \$22.00 and instructed to watch and learn what levels were associated with US delivery and which were not during the ~9 min task. They were told that learning the cue and outcome relationship will be important for doing well on the main task presented later on. Trials consisted of a 3 s CS presentation, 750 ms outcome and a 5-7 s jittered ITI. Each CS threat level was presented for twelve trials in a randomized order. CS+s (levels 4-10) were followed by

the US according to the assigned probabilities shown in Figure 2A. CS-s (levels 1-3) were not followed by the US. Afterwards, ratings of fear and US expectancy were obtained for each CS threat level. Threat conditioning ended when US expectancy ratings showed a linear increasing trend with increasing CS threat, providing evidence of conscious knowledge of differences in CS-US probabilities. All participants were required to meet the criterion before proceeding. Either one or two training sessions occurred.

*2.7.3 Approach-Avoidance acquisition.* For Experiment 2, this step was completed before neuroimaging. Figure 2B provides a schematic of the 1.5 min AA task used for trial and error learning of approach and avoidance responding. While CS threat conditioning successfully established all CS-US relations, this brief training phase involved trial-and-error learning of the basic approach and avoidance contingencies. Five trials with CS- threat level 1 ( $p(\text{US delivery}) = 0.0$ ) were presented followed by five trials of CS+ threat level 10 ( $p(\text{US delivery}) = 1.0$ ). Each trial consisted of a 3 s CS and choice period, 750 ms outcome and a 5-7 s jittered ITI. The goal was to quickly train participants to press the approach button at CS- level 1 and press the avoidance button at CS+ level 10. At CS- level 1, approach produced a \$0.10 reward, while avoidance had no programmed outcome. At CS+ level 10, approach produced the US, while avoidance reduced the threat level from 10 to 1. Training ended when approach occurred at CS- level 1 on 4/5 trials and avoidance occurred at CS+ level 10 on 4/5 trials. All participants were required to meet the criterion before proceeding. Either one or two training sessions occurred.

*2.7.4 Neuroimaging.* In Experiment 2, two consecutive ~10 min imaging runs were completed, separated by a ~3 min break. Participants were given a button box with three buttons arranged vertically and described as #1, #2 and #3. Responses were made with the right thumb. Figure 2B shows the AA task used. For each imaging run, participants began with a stipend of \$2.00. Each trial consisted of a 3 s CS and choice period, 750 ms outcome period and a 4.25-8.25 s jittered ITI. On each trial, a monetary

reward was made available in the presence of a CS threat level displayed on the ‘threat meter.’ The threat meter consisted of ten CS threat levels with higher levels signaling a greater probability of aversive US delivery. Therefore, CS presentations prompted retrieval of different threat memories established during earlier threat conditioning. The CS threat level presented was varied across trials. Approach choices produced the reward or probabilistic US, while avoid choices reduced the threat level and prevented US delivery. Ten baseline trials were presented that involved prompting subjects to press #3. Additionally, twelve trials at each CS threat level were presented that involved making a choice to approach (press #1) or avoid (press #2). Trials were presented in a randomized order. After both imaging runs were completed, ratings of fear and US expectancy were obtained for each CS threat level.

## 2.8 Analyses

*2.8.1 SCR.* The SCR analysis for Experiment 1 was performed following published recommendations (Boucsein et al., 2012) with Ledalab, a Matlab based software that performed event-related analysis of phasic activity associated with the CS onset. Data were log-transformed to normalize data and range corrected to attain statistical normality and reduce error variance (Lykken & Venables, 1971). For each participant, mean percent maximal SCR for the baseline and each CS threat level were calculated. The mean percent maximal SCR represents the mean of the absolute differences between the maximal amplitude deflection 1 s pre-CS onset and the maximal amplitude deflection 3 s post-CS onset. Only trials with an amplitude difference  $> .02 \mu\text{S}$  were considered valid and used to calculate means. Lastly, since lower US probabilities produce better CS+ threat conditioning, our analyses focused on highlighting gross differences between CSs grouped into *High* ( $p(\text{US delivery}) > .50$ ) and *Low* ( $p(\text{US delivery}) < .50$ ) categories as follows: CS+<sub>High</sub> (levels 8-10,  $M p(\text{US delivery}) = .83$ ) and CS+<sub>Low</sub> (levels 4-7,  $M p(\text{US delivery}) = .29$ ), with CS- (levels 1-3,  $M p(\text{US delivery}) = 0$ ). Planned comparisons

evaluating significant differences in SCR among CSs from pretest to threat conditioning were examined using one-sample *t*-tests with a Bonferroni correction,  $p < .05/2$ , and across experimental conditions using *F*-tests,  $p < .05$  (Greenhouse-Geisser corrected), and post-hoc paired one-sample *t*-tests,  $p < .05$ .

*2.8.2 Neuroimaging.* Neuroimaging data analyses for Experiment 2 were performed using SPM 8 (Wellcome Department of Cognitive Neurology, London UK, <http://www.fil.ion.ucl.ac.uk/>).

Preprocessing procedures included reorientation, slice acquisition time correction, coregistration, within-subject realignment, spatial normalization to the standard Montreal Neurological Institute EPI template with resampling to 2 x 2 x 2 mm voxel sizes, and spatial smoothing using a Gaussian kernel (6 mm full width at half-maximum). High pass filtering (1/128 Hz) was applied to the time series of EPI images to remove any low frequency drift in EPI signal. Head motion was restricted to < 3.0 mm in any dimension using the first acquisition as a reference. No participants were excluded.

For first level analysis, individual effects were estimated using the general linear model approach implemented in SPM8. Events of interest modeled included the onsets of baseline trials and each of the ten CS threat levels. All trials contained a response and were used in the analysis. Participant-specific head movement parameters were also modeled as a covariate of no interest. For each participant, ten contrast images were created by subtracting activation associated with the baseline trial from each CS level (i.e., threat levels 1 thru 10). The series of ten contrast images were then carried to a second level for group analyses. A priori planned comparisons were restricted to regions identified in prior investigations on conflict, decision making and foraging. A regions-of-interest (ROIs) mask was created using the Automated Anatomic Labeling atlas (AAL; Tzourio- Mazoyer et al., 2002) of the WFU Pickatlas toolbox (Maldjian et al., 2003) that encompassed the anterior cingulate, ventral, inferior, medial and lateral frontal regions, striatum, insula, and hippocampus. Consequently, second level analyses were restricted to these regions and employed SPM's small volume correction function. An

omnibus  $F$ -test was performed on the series of contrast images to highlight voxels showing significant nonspecific changes with a correction for multiple comparisons set at  $q < .05$  false discovery rate (FDR correction,  $F > 3.01$ ; yielding a voxel  $p < .005$ , uncorrected; Benjamini & Hochberg, 1995; Genovese et al., 2002; Bennett et al., 2009; Lieberman & Cunningham, 2009) and 50 contiguous voxels. This unbiased analysis identified voxels showing significant change with increasing CS threat level without any a priori assumptions about the form of change. Restricted to regions that survived the omnibus  $F$ -test via inclusive masking, vectors of contrast weights were used to differentiate among voxels showing sustained, linear (increasing, decreasing) and nonlinear (i.e., positive and negative quadratic, bimodal; Straube et al., 2009) changes in activation ( $q < .05$  FDR correction, extent threshold of 50 voxels; yielding a voxel  $p < .001$ , uncorrected) with escalating CS threat. As no voxels showed significant linear changes, we only report on quadratic and bimodal changes. All contrast values plotted were extracted from significant peak voxels. The location of voxels with significant activation was summarized by their local maxima separated by at least 8 mm. MNI coordinates are reported. Statistical parametric maps displayed were overlaid onto a standardized reference brain.

*2.8.3 Behavioral.* Significant changes in threat and US expectancy ratings with increasing CS threat were examined within conditions using repeated measures ANOVA with a Bonferroni correction,  $p < .05/2$ . Significant changes in the distribution of approach and avoidance choices with increasing CS threat were examined within conditions using a two-way repeated measures ANOVA and a criterion alpha set at  $p < .05$ .

### **3. Results**

#### *3.1 Experiment 1*



Results are shown in a series of plots in Figures 3 and 4. Findings are arranged with columns representing each experimental condition (CS pretesting, threat conditioning and three sessions of the AA task) and rows representing different dependent measures (ratings, SCR, percent approach/avoidance responses and RTs). For each plot, increasing CS threat appears on the x-axis.

*3.1.1 Ratings.* The first row of Figure 3 shows ratings for perceived threat and US expectancy. Following pretesting, increasing CS threat did not significantly increase ratings of feeling threatened ( $F(9,162) = 0.628, p < 0.77$ ) or US expectancy ( $F(9,162) = 0.593, p < 0.80$ ). After threat conditioning, increasing CS threat significantly increased ratings of feeling threatened ( $F(9,162) = 51.7, p < 0.0001$ ) and US expectancy ( $F(9,162) = 99.9, p < 0.0001$ ), with increases maintained during three sessions of the AA task (all  $p$ 's  $< 0.0001$ ). The significant changes in both ratings offer evidence of knowledge of the different CS-US relations, the avoidance response-outcome contingency and evidence showing the maintenance of the US as an aversive stimulus over sessions.

*3.1.2 SCR.* Table 1 and the second row in Figure 3 highlight successful differential threat conditioning. Significant increases in SCR occurred from pretest to threat conditioning for both CS+<sub>Low</sub> ( $t(18) = 2.63, p = 0.008$ ) and CS+<sub>High</sub> ( $t(18) = 2.09, p = 0.025$ ), but not for CS- ( $t(18) = 0.07, p = 0.47$ ). Following threat conditioning, significant increases in SCR relative to CS- ( $M=0.197, SD = 0.11$ ) were observed for both CS+<sub>Low</sub> ( $M=0.307, SD = 0.167, t(18)=2.83, p = 0.005$ ) and CS+<sub>High</sub> ( $M=0.269, SD = 0.167, t(18) = 1.67, p = .05$ , uncorrected). In addition to highlighting associative learning, these differential changes provided evidence that our US was capable of eliciting a threat response. For the three AA sessions that followed threat conditioning, there was a significant main effect for CS+<sub>Low</sub> relative to CS- (CS+<sub>Low</sub>  $M=0.273, SD = 0.118$ ; CS-  $M= 0.199, SD= 0.110$ ;  $F(1,17) = 5.73, p=0.028$ ) but for CS+<sub>High</sub> (CS+<sub>High</sub>  $M=0.241, SD = 0.150$ ;  $F(1,17) = 1.11 p<0.306$ ). Follow up tests showed significantly greater SCR in session #1 and #2 for CS+<sub>Low</sub> (#1:  $M=0.304, SD = 0.134$ ;  $t(18) = 2.45, p =$

0.012; #2,  $M=0.282$ ,  $SD = 0.178$ ;  $t(18) = 2.57$ ,  $p=0.009$ ) relative to CS- (#1:  $M=0.221$ ,  $SD = 0.109$ ; #2:  $M=0.197$ ,  $SD = 0.158$ ). Neither CS+ showed significant change from the CS- across sessions (CS+<sub>Low</sub>  $F(2,34) = 0.454$ ,  $p=0.639$ ; CS+<sub>High</sub>  $F(2,34) = 0.224$   $p=0.80$ ). A quadratic polynomial provided the best fit of the relationship between SCR and CS threat level, consistent with effects showing peak responses to CS+<sub>Low</sub> threats.

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Insert Table 1 and Figure 3 here

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*3.1.3 Approach-Avoidance.* Figure 4 shows significant changes in the distribution of approach and avoidance choices with increasing CS threat level for three AA sessions. Significant interactions between response type and increasing threat level were found for each session characterized by a decrease in the probability of approach and an increase in the probability of avoidance (#1:  $F(9,360) = 123.8$ ,  $p < 0.0001$ ; #2:  $F(9,360) = 155.4$ ,  $p < 0.0001$ ; #3:  $F(9, 360) = 172.9$ ,  $p < 0.0001$ ). The intersection of the functions lies near level 5 and 6, highlighting the AA transition where >50% of avoidance occurred. This is optimal given that earnings decline rapidly at level 6 (see table insert in Figure 2A). The second row of plots presents mean approach and avoidance RTs for each session. Analyses showed mean reaction times (collapsed across approach and avoidance) changed significantly with increasing CS threat for each session (#1:  $F(9,162) = 8.98$ ,  $p < 0.0001$ ; #2:  $F(9,162) = 14.2$ ,  $p < 0.0001$ ; #3:  $F(9,162) = 13.6$ ,  $p < 0.0001$ ). A quadratic polynomial provided the best fit of the relationship between RTs and CS threat level for each session highlighting that increasing CS threat was associated with an inverted U-shaped RT distribution, with the slowest responses occurring at lower threat levels near the AA transition. What is notable is that choices and RTs peak before threat level 7 which is where uncertainty was greatest [ $p(\text{US delivery}) = .50$ ]. Overall, the changes observed in SCR, choices and RTs

as a function of increasing CS threat are consistent with the idea of changes in choice difficulty and value differences. As value differences between approach and avoidance options decrease with escalating threat, there is increasing conflict along with increased threat, choice difficulty and time needed to make a choice. Importantly, the increases are seen leading up to the transition from approach to avoidance but then show a gradual decline following the transition.

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Insert Figure 4 here

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### 3.2 Experiment 2

The methodology used in Experiment 1 was used successfully during neuroimaging in Experiment 2. Overall, behavioral results from Experiment 1 were replicated in Experiment 2.

3.2.1 *Ratings.* Figure 5A shows ratings for perceived threat and US expectancy for each CS threat level during pretesting, threat conditioning and an average of the two sessions of the AA task completed during neuroimaging. Following pretesting, increasing CS threat did not significantly increase ratings of feeling threatened ( $F(9,261) = 1.0, p = 0.44$ ) or US expectancy ( $F(9,261) = 1.0, p = .44$ ). After threat conditioning, increasing CS threat significantly increased ratings of feeling threatened ( $F(9,261) = 120.9, p < 0.0001$ ) and US expectancy ( $F(9,261) = 171.2, p < 0.0001$ ). Significant increases were also observed for feeling threatened ( $F(9,261) = 407.3, p < 0.0001$ ) and US expectancy ( $F(9,261) = 647.9, p < 0.0001$ ) for the AA task. Consistent with results of Experiment 1, participants exhibited knowledge of the different CS-US relations and the avoidance response-outcome contingency, while the US remained aversive.

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Insert Figure 5 here

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**3.2.2 Approach-Avoidance.** Figure 5B shows behavioral performances on the AA task during neuroimaging were nearly identical to those seen in Experiment 1. The first plot highlights a significant interaction between response type and increasing CS threat level such that there was a decrease in approach and an increase in avoidance ( $F(9,540) = 956.4, p < 0.0001$ ), with threat level  $p(\text{US}) = .33$  as the AA transition ----the CS threat level associated with  $> 50\%$  avoidance. The second plot shows individual subject AA transition data and reveals that the vast majority of subjects transitioned at the threat level  $p(\text{US}) = .33$ . The third plot highlights changes in approach and avoidance RTs, with mean RTs showing significant change with increasing CS threat ( $F(9,261) = 12.7, p < 0.0001$ ) with slowest responses occurring near the AA transition. A quadratic polynomial again provided the best fit of the relationship between RTs and CS threat level. In addition, the AA transitions and RT slowing were not centered where uncertainty was greatest [ $p(\text{US})$  delivery = .50]. Overall, the changes observed in choices and RTs as a function of increasing CS threat are consistent Experiment 1 and choice difficulty and value difference accounts.

**3.2.3 Brain activation.** Figure 6 presents plots highlighting positive and negative quadratic and bimodal changes in activation as a function of increasing CS threat (Table 2). A secondary  $y$  axis is included to facilitate comparisons of activation changes with the increasing probability of aversive US delivery (thick transparent white line) and the increasing probability of avoidance behavior observed (heavy dotted line—adapted from Figure 5B). Parametric maps and the plot in Figure 6A highlight negative quadratic (inverted U-shaped) changes in activation in pregenual and dorsal anterior cingulate, dorsal and ventral caudate and areas encompassing anterior insula and inferior frontal brain regions. The changes in activation are consistent with an inverse ‘value difference’ account in which signal *increased* as the difference between values of choices *decreased*. An important feature of this display is it shows

activation scales with changes in value differences and AA behavior. Value differences on the approach endpoint of the AA continuum are initially large but gradually decrease and then increase nearing the avoidance endpoint. Also significant was many regions showed similar changes in activation and peak activation occurred at the same CS threat level. Most importantly, peak activation in clusters encompassing ACC and dmPFC regions occurred at a threat level that just preceded the AA transition. It is also worthy to note the AA transition and peak activation occurred below the uncertainty threshold, where  $p(\text{US delivery})$  was .50, which underscores that changes in activation are not solely driven by uncertainty but instead by the relative value differences between choice options.

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Insert Figure 6 and Table 2 here

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Parametric maps and the plot in Figure 6B highlight positive quadratic (U-shaped) changes in activation in ventromedial prefrontal cortex (vmPFC) and left dorsolateral prefrontal cortex (DLPFC). These findings are consistent with a ‘value difference’ signal in which signal *increased* as the difference between values of choices *increased*. Regional activation was highest nearer the ends of the threat meter where value differences were greatest and outcomes associated with approach and avoidance were far more predictable. Along similar lines, Figure 6C shows a bimodal change in activation in the orbitofrontal (OFC) and ventral hippocampus where activation peaked and declined near the AA threshold. Interestingly, these results occurred regardless of outcome type - positive (earn money) or negative (avoid money loss) reinforcement. Once again, the changes in activation were remarkably consistent across regions and the relatively lowest activation occurred at a threat level that just preceded the AA threshold. Finally, plots in 6A and 6B together highlight an inverse parallel relation between

dorsal and ventral frontal regions and changes in activation that align with a transition from approach to avoidance.

#### **4. Discussion**

This investigation examined the underlying brain mechanisms supporting transitions along the approach-avoidance continuum under conditions of increasing threat. Behavioral and functional neuroimaging experiments were conducted using an AA task in which a fixed monetary reward was available in the presence of different CSs signaling variable probabilities of US delivery. Approach produced reward or a probabilistic US while avoidance prevented US delivery. Our major findings revealed that increases in CS threat reliably shifted approach-avoidance behavior and produced inverted U-shaped changes in decision times, SCR, and activation in pregenual ACC, dACC/dmPFC, striatum, anterior insula and inferior frontal regions. Ventral frontal regions and the hippocampus showed opposite U-shaped changes in activation. Importantly, both frontal activation patterns showed a close correspondence with transitions from approach to avoidance. These new findings suggest parallel dorsal-ventral frontal circuits support gating of human approach-avoidance behavior where dACC/dmPFC signals inversely correlate with value differences between approach and avoidance contingencies while ventral frontal signals correlate with the value of predictable outcomes.

The precise functional contributions of dACC/dmPFC to decision making have been an area of intense research and debate for some time. A number of theoretical perspectives have emerged that emphasize involvement in detecting and monitoring conflict and errors (Botvinik, 2007), comparing and integrating stimulus information (Talmi et al. 2009; Park et al., 2011), regulating emotional valence (Amemori & Graybiel, 2012), tracking alternative choices during foraging (Kolling et al., 2012, 2014; Mobbs et al., 2013), representing choice difficulty in foraging situations (Shenhav et al., 2014) and

arbitrating value differences between choice options (Basten et al., 2010; Philiastides et al., 2010; Hare et al., 2011). Although the present findings do not explicitly favor one perspective over another, they are generally supportive of conflict, choice difficulty and value difference views. However, the predictions offered overlap considerably making many views complementary rather than competitive. The behavioral findings from our two independent studies offer important convergent evidence that decreasing value differences between choice options increases conflict, choice difficulty, threat responses and time needed to make a decision.

Accounting for the present findings in terms of arbitrating changes in value differences or choice difficulty may not be the only explanation for the AA transition observed. The systematic changes in activation may reflect anticipation of aversive outcomes, which has also been shown to engage the anterior insula, ventral striatum, DLPFC and dACC (Jensen et al., 2003; Paulus et al., 2003; Nitschke et al., 2006; Samanez-Larkin et al., 2008). In one study on anticipatory anxiety, Straube et al., (2009) did observe an inverted U-shape response in ventral ACC. However, while anticipation may be a viable account of increasing activation *leading up* to the AA transition, it is inconsistent with the gradual decreases in activation *after* the AA transition. Presumably, when avoidance responding consistently prevents aversive outcomes, anticipation of aversive outcomes and associated activation would drop precipitously rather than decline slowly. Furthermore, regional activation associated with anticipation occurs because participants in prior studies do contact aversive outcomes, whereas in our task contact with aversive outcomes is prevented. The systematic changes in dACC/dmPFC activity may also reflect changes in CS threat appraisal and fear expression associated with changes in the probability of US delivery (Rushworth et al., 2007; Etkin et al., 2011; Shackman et al., 2011; Kalisch and Gerlicher, 2014). Support for this alternative explanation can be found in one fear-conditioning study that reported linear increases in dACC activation from a CS- to CS+s delivering intermittent ( $p(\text{US}) = .50$ ) and

continuous reinforcement (Dunsmoor et al., 2007). However, we observed a negative quadratic change with increasing  $p(\text{US})$  delivery. Although an interpretation based on strictly on US probability falls short, it is plausible that following the AA transition successful avoidance altered the function of CS+s signaling higher probabilities of US delivery leading to reduced regional activation (Schlund et al., 2015). In large part, our findings showing U shaped changes in vmPFC activation with CS threat increases is consistent with other investigations that show decreased activation when outcomes become less predictable, which occurs under increasing risk (Schonberg et al., 2012) and transitioning from reinforcement to extinction conditions (Schlund et al., 2012). There is also evidence for increases in vmPFC activation during learning under positive and negative reinforcement contingencies as outcomes become more predictable (Schlund & Ortu, 2010; Schlund et al., 2011).

Findings highlighting systematic changes in regional activation associated with AA transitions extend research on value-guided decision making in ways that have implications for basic and clinical research. Studies on foraging use tasks in which the value of choice options and associated value differences stem from appetitive contingencies. Many report ACC activation correlates with the value of the unselected choice option (Hayden et al., 2011; Kolling et al., 2012, 2014; Mobbs, 2013) but other evidence points to value differences and choice difficulty (Shenhav et al., 2014). In the present investigation, the value of choice options and associated value differences stem from appetitive and aversive contingencies. When evaluated against results of foraging studies, our findings showing quadratic changes in dACC activation represents an important systematic replication that supports generalization of value difference and choice difficulty views to account for AA transitions. Another significant basic research finding of the present investigation is results highlighting contrasting activation patterns in dorsal and ventral brain regions. As value differences between approach and avoidance decreased we found an increase in dorsal frontal activation and a decrease in ventral frontal



activation. We interpreted these differences in terms of dACC/dmPFC signals correlating with value differences between approach and avoidance contingencies and ventral frontal signals correlating with the value of predictable outcomes. Moreover, regional changes corresponded with the transition from approach to avoidance, such that the highest and lowest activation preceded a shift. These new findings suggest parallel dorsal-ventral frontal circuits support gating of human approach-avoidance behavior. It remains to be determined whether similar effects occur during foraging tasks that use appetitive contingencies or whether they are restricted to AA contexts that use both appetitive and aversive contingencies. Finally, the present findings have relevance to our understanding of avoidance in psychopathology. An emphasis on value difference signals in dorsal and ventral frontal cortices in gating approach and avoidance aligns well with value-oriented clinical theories of anxiety and treatments that emphasize re-evaluating or re-appraising stimuli or learning to perform more adaptive cost-benefit analyses (Mogg & Bradley 1989; Clark & Beck, 2010; Sheppes et al., 2015). Consequently, the application of a value-guided decision-making framework may facilitate integration of basic research on the neurobiology of valuation and decision-making with value-focused theories of anxiety and interventions (e.g., Kirk et al., 2014).

Future investigations are needed to address a number of potential limitations that may limit generalization of findings. At a methodological level, threat related responses might be enhanced or altered with more aversive US, such as electric shock or phobic stimuli. Preparing participants for the task requires threat conditioning and approach-avoidance training which can be time consuming. However, the gains in experimental control associated with precisely defining CS-US relations and tie to the fear-conditioning literature seem to outweigh any costs. We would also argue that while somewhat artificial, threat conditioning is experiential and more akin to how fears/threats emerge from real-life negative experiences (Vervliet & Raes, 2013). The extent to which experiential learning of CS-US

relations differs from using instructions remains an area for future investigations. Inclusion of other independent physiological measures such as pupil dilation or fear-potentiated startle responses may also be informative. Restricting choices to within a small time window may also artificially truncate the time normally given to AA arbitration. How value differences associated with different reward and threat magnitudes and probabilities shift AA transitions and regional activation also needs to be explored. For example, value differences in this investigation were established by holding reward magnitude and US (loss) magnitude constant while manipulating US probability. Whether similar activation patterns occur when reward magnitude and US probability are held constant while US (loss) magnitude varies is unclear. These conditions remove uncertainty associated with US probability and would provide an important test of how much US probability and US magnitude contribute to changes in regional activation. Future research is also needed that explores individual differences. In addition to examining anxiety level and approach-avoidance tendencies, behavioral economics suggests individual differences in utility, diminishing sensitivity or probability weighting functions may be important factors that modulate AA transitions (Tversky & Kahneman, 1992; Camerer & Ho, 1994; Gonzalez & Wu, 1999).

## 5. Conclusion

In sum, these new findings suggest parallel dorsal-ventral frontal circuits support gating of human approach-avoidance behavior where dACC/dmPFC signals inversely correlate with value differences between approach and avoidance contingencies while ventral frontal signals correlate with response-outcome predictability. Findings highlighting systematic changes in regional activation associated with AA transitions provide a bridge between research on brain mechanisms of value-guided decision-making and value-focused clinical theories of anxiety and interventions.

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## **8. Conflict of Interest**

None declared

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## Figure Captions

*Figure 1. Theoretical changes in dACC/dmPFC activation over the approach-avoidance continuum.*

The x-axis shows relative differences in values associated with approach for reward (Rew: appetitive contingency) and threat avoidance (Threat: aversive contingency). Functions plotted are general representations of different theoretical perspectives. The shaded area in the middle of plots represents the approach-avoidance transition area. **[A]** *Integration/Comparator* views suggest activation occurs whenever a choice requires comparison/integration of option values. *Foraging* views suggest monotonic increases in activation that scale with the value of alternative choices. *Conflict* views predict peak activation when values conflict. *Choice difficulty* and *value difference* views both predict negative quadratic changes. **[B]** Predicted inverse value difference signal in dACC/dmPFC---(solid line) decreases in reward-threat value differences along the x-axis produce negative quadratic changes in activation. Predicted value difference signal in ventral frontal regions---(dashed line) decreases in reward-threat value differences along the x-axis produce positive quadratic changes in activation.

*Figure 2. Schematic of threat acquisition and Approach-Avoidance (AA) task.* **[A]** Prior to neuroimaging, participants completed threat conditioning which involved pairing increasing ‘levels’ on a vertical bar with increasing probabilities of US delivery (see table insert). Each trial presented a “NOW” cue (a CS) on the bar followed 3 s later by the probabilistic US (see table insert). Threat levels 1-3 served as CS-s, while levels 4-10 served as CS+s representing escalating threat. **[B]** Main display of the AA task used in Experiment 1 and 2. On each trial, a reward and a threat level were presented. Participants were given a choice between approach (Press #1), which produced \$0.10 or the probabilistic US, and avoid (Press #2), which prevented US delivery. During baseline trials, participants were prompted to “Press #3”. Trials consisted of a 3 s period during which the CS threat level was displayed

and choice occurred, followed by a 750 ms outcome period and jittered ITI. The upper right table shows earnings decline for approach choices beginning at threat level 6.

*Figure 3. Experiment 1 (behavioral) ratings and SCR.* Plots are arranged by conditions: pretesting, threat conditioning and three consecutive sessions of the Approach-Avoidance (AA) task. Increasing CS threat level is represented as increasing  $p(\text{US delivery})$  on the x-axis. **[A]** Increases in ratings of feeling threatened and US expectancy with increasing CS threat, indicating successful threat conditioning. Moreover, plots show the increases were maintained during three sessions of the AA task. **[B]** Successful differential threat conditioning produced significant increases in SCR at the Low Threat level relative to CS-. Results show inverted U-shape changes in SCR occurred after threat conditioning and this effect was maintained for AA sessions 1 and 2. A quadratic polynomial fitting highlights the relationship between SCR and CS threat level. (Horizontal bars represent significant differences within and between conditions, see Table 1. Vertical bars represent 95% confidence intervals.)

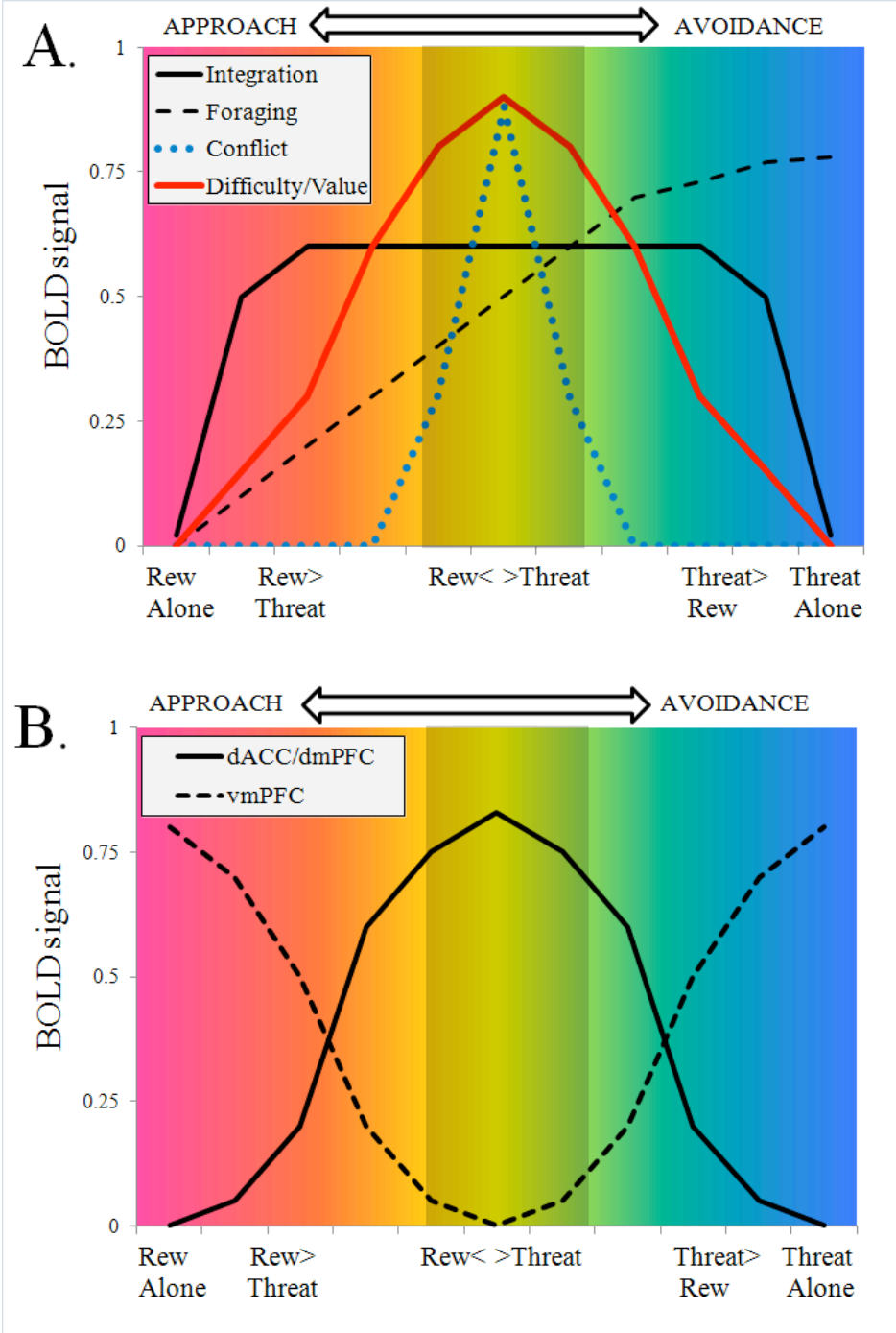
*Figure 4. Experiment 1 (behavioral) AA task performances.* Plots highlight changes in AA choices over three sessions. Increasing CS threat level is represented as increasing  $p(\text{US delivery})$  on the x-axis. **[A]** Plots highlight approach and avoidance gradients. Results show decreases in approach and increases in avoidance as CS threat increases. The intersection of the functions highlights the AA transition, where approach gave way to avoidance. **[B]** Time taken to choose whether to approach or avoid during three sessions. Increasing CS threat produced an inverted U-shaped distribution of RTs with the slowest responses midway, near the AA transition. A quadratic polynomial fitting highlights the relationship between mean decision times and CS threat level. (Vertical bars represent 95% confidence intervals.)

*Figure 5. Experiment 2 (fMRI) ratings and AA task performances.* **[A]** Increases in ratings of feeling threatened and US expectancy with increasing CS threat during and following threat conditioning. Results highlight successful differential threat conditioning prior to neuroimaging and its maintenance after neuroimaging. **[B]** The left plot shows approach and avoidance gradients, revealing decreases in approach and increases in avoidance as CS threat increased. The intersection of gradients highlights the AA transition or > 50% avoidance at  $p(\text{US}) = .33$ . The middle plot shows AA transitions for individual participants. Most transitions occurred at  $p(\text{US}) = .33$ . The right plot shows increasing CS threat produced an inverted U-shaped distribution of decision times (i.e., RTs), with the slowest responses midway near the AA transition. A quadratic polynomial fitting highlights the relationship between mean decision times and CS threat level. (BL= baseline trials used for imaging analyses. Bars represent 95% confidence intervals.)

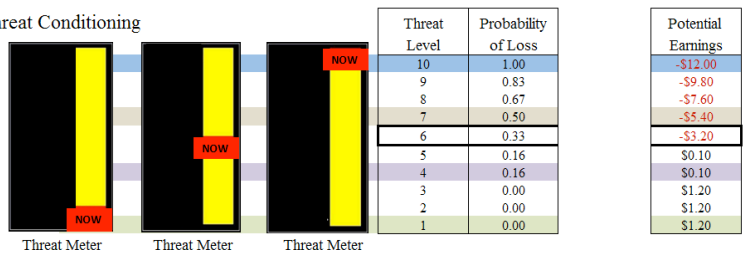
*Figure 6. Experiment 2 regional changes in brain activation with increasing CS threat.* Plots highlight regional changes in contrast values as a function of increasing CS threat ( $p(\text{US})$ ). To facilitate brain-behavior comparisons, a secondary y axis is used to highlight the increasing probability of aversive US delivery (thick transparent white line) and the increasing probability of avoiding (heavy white dotted line---from avoidance function shown in Figure 5B). For display, functions were normalized to have a zero onset at threat level 1. Triangles on the x-axis are provided to delineate the AA transition (blue) and uncertainty threshold (red:  $p(\text{US})$  delivery = .50). **[A]** Negative quadratic changes in activation were observed with increasing CS threat in the ACC, caudate, anterior insula and inferior frontal regions. Functions are similar across regions and peak activation occurred at a lower threat level than the AA transition and uncertainty thresholds. **[B]** Positive quadratic changes in activation with increasing CS threat in ventromedial prefrontal cortex and left dorsolateral prefrontal cortex. **[C]** Bimodal changes in



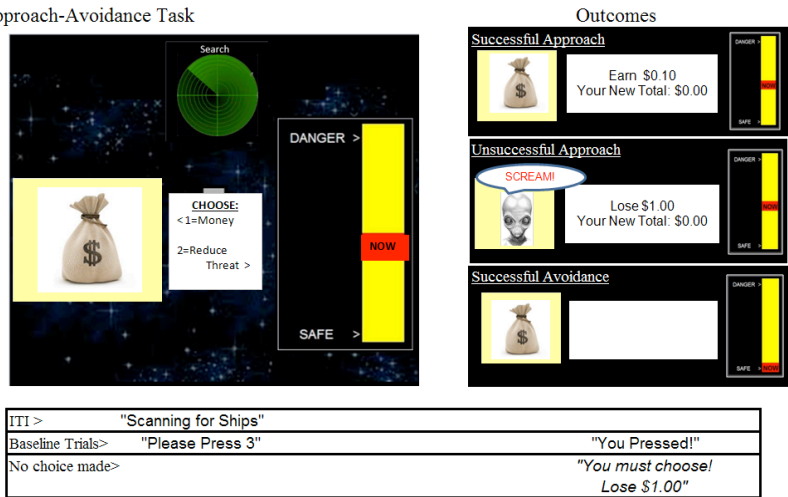
activation were observed with increasing CS threat in the orbitofrontal cortex and left ventral hippocampus. (pg=pregenual; d=dorsal; dm=dorsomedial, vm=ventromedial; R=right; L=Left).



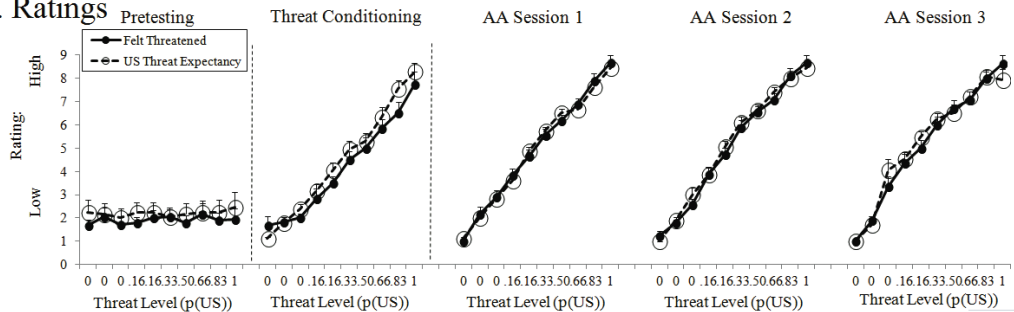
A. Threat Conditioning



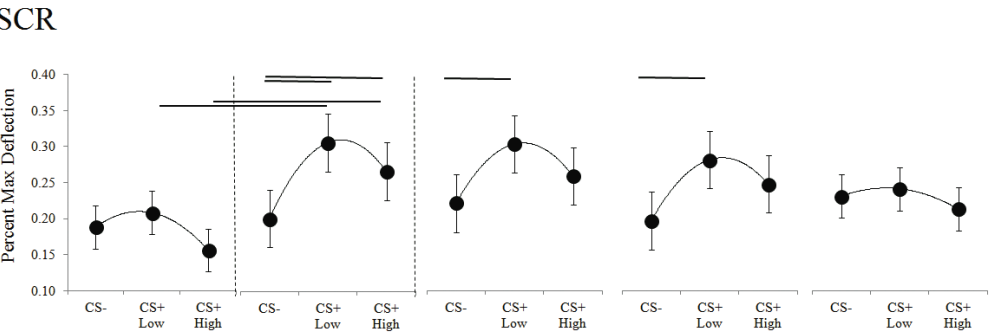
B. Approach-Avoidance Task



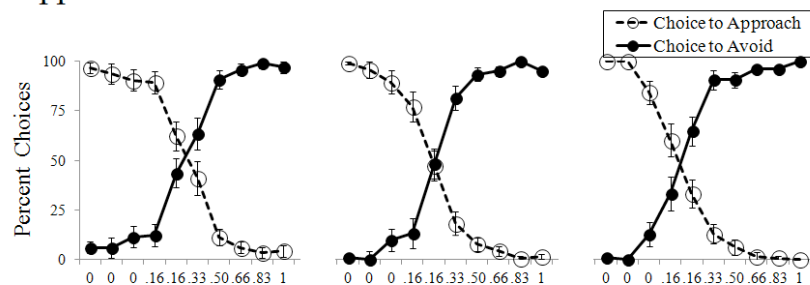
A. Ratings



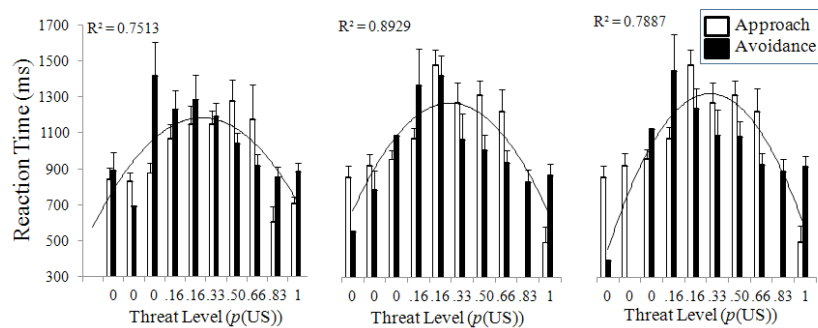
B. SCR



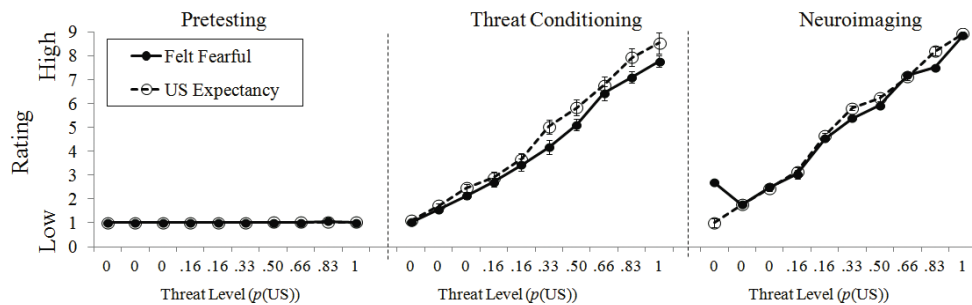
A. Approach-Avoidance Choices



B. Approach-Avoidance Decision Times



A. Ratings



B. Approach-Avoidance Task Performance

