How distributed subcortical integration of reward and threat may inform subsequent approach-avoidance decisions

Abbreviated title: Reward-threat integration in approach-avoidance

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ABSTRACT

Healthy and successful living involves carefully navigating rewarding and threatening situations by balancing approach and avoidance behaviours. Excessive avoidance to evade potential threats often leads to forfeiting potential rewards. However, little is known about how reward and threat information is integrated neurally to inform either approach or avoidance decisions. In this preregistered study, participants (N=31, 17F) made approach-avoidance decisions under varying reward (monetary gains) and threat (electrical stimulations) prospects during functional MRI scanning. In contrast to theorized *parallel subcortical* processing of reward and threat information before cortical integration, Bayesian Multivariate Multilevel analyses revealed subcortical reward and threat *integration* prior to indicating approach-avoidance decisions. This integration occurred in the ventral striatum, thalamus, and bed nucleus of the stria terminalis (BNST). When reward was low, avoidance decisions dominated, reflected in stronger reactivity to threat prior to indicating avoidance decisions across these regions. In addition, the amygdala exhibited dual sensitivity to reward and threat. While anticipating the outcome of approach decisions, characterized by elevated risk of electrical stimulation, increased threat-related activity within the salience network (dorsal anterior cingulate cortex, thalamus, periaqueductal gray, BNST) was observed. Conversely, anticipating the outcome of avoidance decisions, marked by reduced reward potential, was associated with suppression of reward-related activity in the ventromedial prefrontal cortex and ventral striatum. These findings shed light on the temporal dynamics of approach-avoidance decision-making. Importantly, they demonstrate the role of subcortical integration of reward and threat information in balancing approach and avoidance, challenging theories positing predominantly separate subcortical processing before cortical integration.

INTRODUCTION

Healthy and successful living involves carefully navigating rewarding and threatening situations by adopting an appropriate balance between approach and avoidance behaviours. Disruption of this balance can result in severe consequences, as observed in anxiety-related disorders and addiction (American Psychiatric Association, 2013). In approach-avoidance decision-making, the weighing of potential reward and threat prospects is pivotal (Corr, 2013). However, little is known about how this weighing is neurally represented to inform approach or avoidance decisions. In this study, we leveraged Bayesian Multivariate Multilevel (BMM) analyses on trial-by-trial BOLD fMRI data to investigate how distributed processing and integration of reward and threat information in the human brain contribute to approach-avoidance decision-making.

Human neuroimaging studies and recent theoretical frameworks suggest that reward and threat information is processed in distinct *parallel* subcortical streams, followed by reward-threat *integration* in cortical regions (Yacubian et al., 2006; Aupperle and Paulus, 2010; Basten et al., 2010; Park et al., 2011; Schlund et al., 2016; Zorowitz et al., 2019; Azab and Hayden, 2020; Livermore et al., 2021). For example, the ventral striatum (vStriatum) plays a crucial role in processing positive value and rewards (Talmi et al., 2009; Aupperle and Paulus, 2010; Basten et al., 2010; Bartra et al., 2013), potentially driving approach behaviour (Alvarez & Ruarte, 2001; Beaufour et al., 2001; Pedersen et al., 2021). Conversely, the amygdala and bed nucleus of the stria terminalis (BNST) are widely recognized for their pivotal roles in threat processing (Shackman and Fox, 2016; Abivardi et al., 2020; Hur et al., 2020; Hulsman et al., 2021c) and facilitation of avoidance behaviour (Ch'ng et al., 2018; Duque-Wilckens et al., 2018; Giardino et al., 2018; Miller et al., 2019; Hu et al., 2020). Value signals, indicating reward and threat potential, subsequently need to be integrated to inform decision-making, as previously demonstrated in cortical regions including the ventromedial prefrontal cortex (vmPFC) and dorsal anterior cingulate cortex (dACC) (Basten et al., 2010; Park et al., 2011; Schlund et al., 2016; Zorowitz et al., 2019; Azab and Hayden, 2020).

However, preclinical studies have demonstrated that reward and threat processing may be *intertwined* at the neuronal level already within subcortical regions, as well as with processing of opposite valence occurring in neighbouring cells, e.g., within subregions of the amygdala (Gentry et al., 2016; Burgos-Robles et al., 2017; Hamel et al., 2017; Beyeler et al., 2018). Moreover, recent rodent studies have shown that subcortical regions, including the central nucleus of the amygdala (CeA) and nucleus accumbens (NAcc) can trigger both approach and avoidance motivation depending on the context and input received from other structures (Warlow et al., 2020; Zhou et al., 2022) and that regions of the thalamus respond particularly to situations requiring integration, such as approach-avoidance conflict (Engelke et al., 2021). This aligns with recent human work showing that regions of the salience network (thalamus, periaqueductal gray, dACC, and anterior insula) are sensitive to both rewards and threats (Aupperle et al., 2015; Schlund et al., 2016; Moughrabi et al., 2022). Strikingly, however, none of the aforementioned human studies investigated how the interplay between reward and threat is represented across these brain regions and how this balance shifts upon decisions to approach or avoid.

To unravel how processing and integration of reward and threat across the brain are linked to approach-avoidance decisions, participants performed a Fearful Avoidance Task (Hulsman et al., 2021a) in the MRI scanner. In this task, participants made approach-avoidance decisions under varying prospects of reward (monetary gain) and threat (electrical stimulation). In the current study, we hypothesized based on current human literature, that prior to approach, valence-specific activations would occur in brain regions most strongly related to appetitive processing (vStriatum, vmPFC). Conversely, prior to avoidance, we expected activations in brain regions traditionally linked to defensive responding (amygdala, BNST). Additionally, we expected that the vmPFC and dACC play a crucial role in reward-threat value integration. Finally, following approach-avoidance decisions we expected valence-specific activations tracking upcoming reward and threat prospects.

MATERIALS AND METHODS

Research questions, hypotheses, and planned analyses were preregistered at the Open Science Framework: https://osf.io/7sm9k (Hulsman et al., 2021b) prior to data analyses. All data and code will be available at the Donders Institute for Brain Cognition and Behaviour repository upon publication: https://doi.org/10.34973/gxr8-9f24. Supplementary information is available at the Open Science Framework: https://osf.io/hbjp5.

Participants

The recruited sample consisted of 31 participants (17 females, M_{age} = 23.45, SD_{age} = 3.33). Three participants were a priori excluded from the MRI analyses due to a lack of avoidance behaviour (<10%, see also Hulsman et al., 2024). As a result, planned contrasts of approach vs avoid trials could not be carried out in these participants. Exclusion of these participants led to a final sample size of N=28 (15 females, M_{age} = 23.25, SD_{age} = 3.27). Inclusion criteria were 18-35 years of age, MRI eligible, normal/corrected-to-normal vision, sufficient English or Dutch comprehension skills, no psychiatric, no neurological or cardiological disease/treatment, no use of psychotropic medication, no current drug or alcohol abuse, and no epilepsy. Participants received EUR 10 for participation and an additional bonus between EUR 0-5 depending on their performance in the Fearful Avoidance Task (described below). All participants were MRI eligible and provided written informed consent. This study was carried out in compliance with the declaration of Helsinki and approved by the local ethics committee (CMO Arnhem-Nijmegen).

Procedure

Participants were informed that they had the opportunity to earn a monetary bonus based on their behaviour in the Fearful Avoidance Task (FAT, Hulsman et al., 2021a). They were asked to write down 10 random numbers, which would later be linked to specific trial numbers using a mathematical formula that was disclosed to the participants only after the experiment. If they

received a monetary reward during these trials, they would receive the corresponding sum as a bonus, capped at a maximum of EUR 5.

Next, participants underwent titration procedures to determine their individual reward and threat levels for the Fearful Avoidance Task. Initially, to establish shock intensity at a point of maximum discomfort without causing pain, participants underwent a standardized *shock work-up procedure* consisting of five shock administrations (Klumpers et al., 2010). Each shock was rated on a scale ranging from 1 (not painful/annoying) to 5 (very painful/annoying). Intensities were adjusted gradually to attain a subjective level that as maximally uncomfortable without being painful (aiming for a 4 on the 5-point scale). Electric shocks were delivered via two Ag/AgCl electrodes attached to the distal phalanges of the middle and ring finger of the right hand using a MAXTENS 2000 (Bio-Protech) device. Shock duration was 250ms at 150Hz, and intensity varied in 10 intensity steps between 0-80mA.

Next, we conducted a *reward-threat titration procedure* to determine the monetary reward required for individuals to accept the risk of receiving an electric shock of the predetermined shock work-up intensity. Amounts between EUR 0.20 and EUR 10 were presented in semi-random order. For each amount, participants were asked whether they would be willing to risk receiving electrical stimulation. No actual shock reinforcement was administered throughout this entire procedure. Participant's indifference point (M = 1.17, SD = 1.84) was subsequently used to calculate the reward values for the ensuing FAT (described below).

Finally, the Fearful Avoidance Task (FAT, Hulsman et al., 2021a) was employed to evaluate active approach-avoidance behaviour under competing reward (monetary gains) and threat (electric shocks) prospects. In this study, participants performed an adapted version of the FAT (see next section), optimized for use in the MRI scanner.

Fearful Avoidance Task (FAT)

Participants received on-screen instructions for the task. Each trial consisted of a cascade of three phases (see Figure 1A). In the *decision phase* participants were confronted with a

combination of reward and threat. The reward level was a monetary amount displayed in numbers below the avatar and was relative to the individual's indifference point (IP) either low (IP - 40-50%), medium (IP ± 5%), or high (IP + 40-50%). The threat levels were displayed with different avatars (Figure 1B). In total, there were three threat levels associated with different durations of electrical shock (low: 5ms, medium: 35ms, and high: 250ms). Reward and threat were combined in a 3 x 3 full factorial manner, resulting in nine combinations of reward and threat. After trial onset, participants had 2.5 seconds to decide to approach or avoid by pulling the joystick towards themselves or pushing the joystick away from themselves, respectively. As confirmation of a timely response (<2.5s) a white line appeared below the reward for the remainder of the decision phase and the subsequent outcome anticipation phase.

Next, a 5-7s *outcome anticipation phase* started. In this phase, the avatar and monetary amount remained on the screen while participants anticipated the outcome of their decision.

Finally, participants received one of three possible outcomes: positive, negative, or neutral. In a positive outcome, the avatar offered a stack of banknotes. In a negative outcome, the avatar drew a gun and shot. Additionally, participants received an electric shock with a duration that corresponded to the threat level symbolized by the avatar. During a neutral outcome, the avatar kept its hands behind its back, resulting in omission of both reward and threat. The probability of receiving a particular outcome depended on the decision that participants made (Figure 1C). Avoidance led to a 40/40% chance of receiving a positive or negative outcome and a 20% chance on receiving a neutral outcome, whereas approach led to an 80% chance of receiving a neutral outcome and a 10/10% chance of receiving a positive or negative outcome. Participants were instructed that late responses (>2.5s) always led to the negative outcome, i.e., getting shot and receiving an electrical shock of a duration that was symbolized by the avatar. After participants received the outcome, a fixation cross was displayed during the inter-trial interval (6-8s).

Participants received explicit instructions regarding the association between the avatar and the corresponding threat level, as well as the outcome probabilities of approach and avoidance decisions. These contingencies were all clearly explained to the participants before starting the task, and comprehension was verified during a short practice session of 9 trials. The association between avatars and threat levels was counterbalanced across participants. In total, participants completed 90 trials (10 trials for each combination of reward and threat).

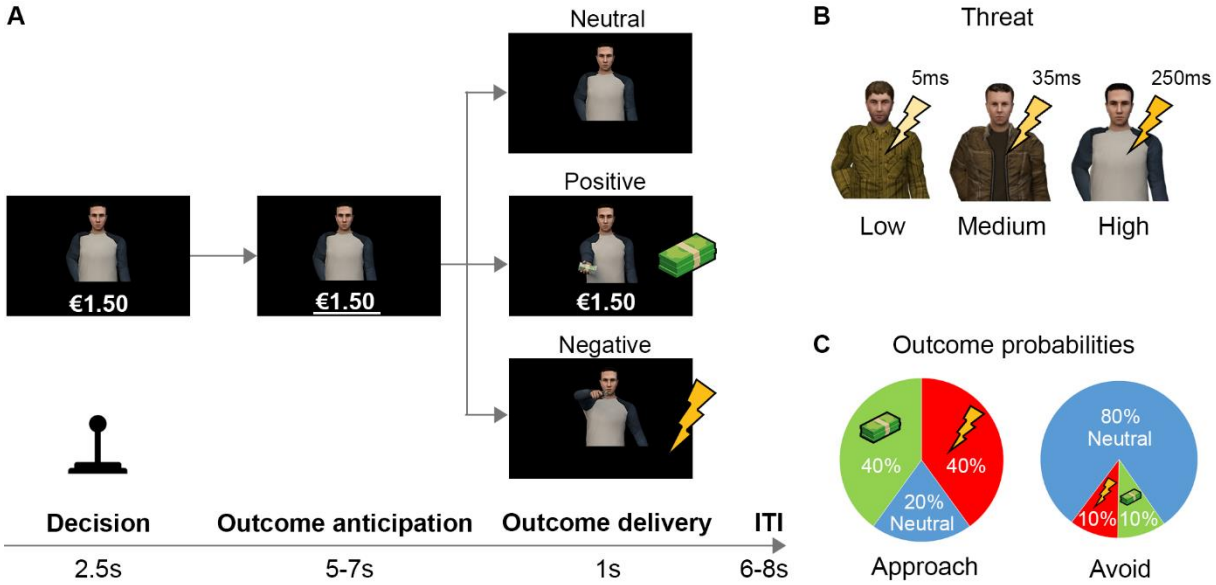

Figure 1. Overview of the Fearful Avoidance Task (FAT). (A) Example of the FAT trial structure. In each trial, participants were first confronted with a combination of reward (displayed in text) and threat (signalled by the avatar). Participants had 2.5s to decide to approach or avoid by pulling the joystick towards themselves or pushing it away, respectively. Next, they anticipated the outcome of their decision. Finally, the outcome of their decision was displayed. After receiving the outcome, a fixation cross was presented during the inter-trial interval (ITI). **(B)** Overview of threat levels: three distinct avatars signalled shock duration. Contingencies between avatars and threat levels were counterbalanced across participants. **(C)** Overview of outcome probabilities for approach and avoidance decisions.

MRI acquisition

Data was acquired on a 3T MAGNETOM PrismaFit MR scanner (Siemens AG, Healthcare Sector, Erlangen, Germany) using a 32-channel head coil. A T1-weighted scan was acquired in the sagittal orientation using a 3D MPRAGE sequence (TR=2000ms, TE=3.03ms, 192

sagittal slices; 1.0mm isotropic voxels; FOV=256mm). T2-weighted volumes were acquired using a multi-band multi-echo (MB3ME3) sequence, a fast sequence designed for whole brain coverage with reduced artefacts and signal dropout in medial prefrontal and subcortical regions (Cohen et al., 2018; Fazal et al., 2023) (TR = 1500ms, $TE_{1\text{-}3}$ = 13.4/34.8/56.2ms, flip angle = 75°, 51 sagittal slices; 2.5mm isotropic voxels).

Behavioural analyses

First, we verified whether the data adhered to the preregistered inclusion criteria, which stipulated a maximum of 50% missing responses and absence of atypical response patterns as defined by Hulsman, Klaassen, et al., (2021). Atypical response patterns refer to behaviour indicating that the participant may not have comprehended the task correctly or did not perform the task seriously (e.g., when participants avoided substantially more on low threat trials than high threat trials, see supplement for a detailed description of atypical response patterns). All participants met these inclusion criteria.

To investigate the effect of reward, threat, and their interaction on the decision (approach/avoid) that participants made, we ran a Bayesian multilevel model. For full model specifications, see equation (1) below. Other model specifications were as described in the next section.

$$Decision_{\ approach\ vs\ avoid} \sim Reward * Threat + \ (1 + Reward * Threat \mid Subject) \qquad (1)$$

Bayesian multilevel analyses (general)

As preregistered (Hulsman et al., 2021b), throughout behavioural and fMRI analyses, we employed Bayesian multilevel models. Bayesian multilevel models were executed using R (Version 4.2.1; R Core team, 2022) within RStudio (Version 2022.12.0; RStudio Inc., 2009-2022) using the brms package (2.18.0, Bürkner, 2013 and Carpenter et al., 2017). All Bayesian multilevel models adhered to the following configurations: continuous predictors were standardized, and categorical predictors were coded using sum-to-zero contrasts. All models

included a maximal random effects structure, consisting of a random intercept for each participant along with random slopes for all predictors and their interactions. Models with a binomial dependent variable (i.e., decision: approach/avoid) were modelled using a Bernoulli distribution, whereas models with continuous dependent variables (i.e., fMRI beta values) were modelled using a Gaussian distribution. Models were fitted using 4 chains with 4000 iterations each (2000 warm-up). A coefficient was deemed statistically significant when the associated ≥95% posterior credible interval was non-overlapping with zero. As recommended for analyses with an effective sample size <10.000 (Kruschke, 2014) this was supplemented with 90% posterior credible intervals when the 95% intervals were overlapping with 0, given that these intervals may yield more stable results (Makowski et al., 2019). These latter results are reported as trends when the 90% interval was non-overlapping with zero. Planned comparisons were conducted using the emmeans package (Lenth et al., 2018).

fMRI analyses

The fMRI data were processed using SPM12 (Wellcome Trust Centre for Neuroimaging, London, UK). Functional scans were combined to a single image with a PAID-weighting method (Poser et al., 2006), co-registered to the anatomical scan, and normalized to the Montreal Neurological Institute (MNI) 152 T1-template. The normalized images (2mm isotropic) were then smoothed with an isotropic 3D Gaussian kernel with 6mm full width at half maximum (FWHM).

Our preregistered regions of interest (ROIs, see Figure 2) included the anterior insula (Shirer et al., 2012), amygdala (Rolls et al., 2020), bed nucleus of the stria terminalis (Avery et al., 2014), dorsal anterior cingulate cortex (Shirer et al., 2012), periaqueductal gray (Lojowska et al., 2015), thalamus (Rolls et al., 2020), ventral medial prefrontal cortex (Rolls et al., 2020), and ventral striatum (Piray et al., 2017).

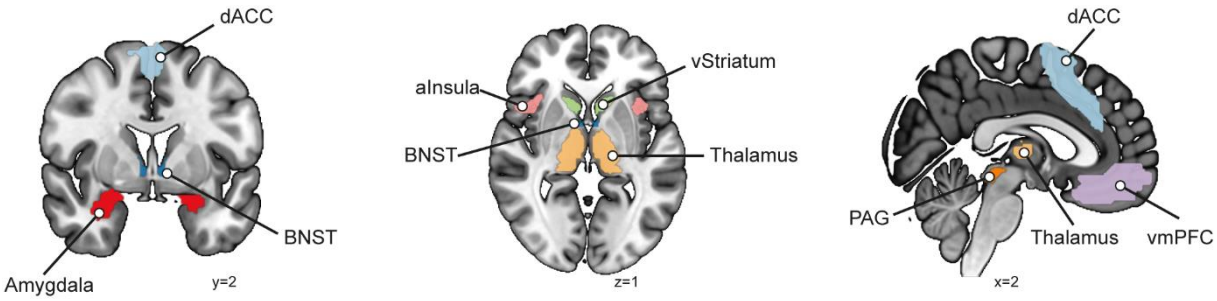

Figure 2. Regions of interest (ROIs). aInsula = anterior insula, amygdala, BNST = bed nucleus of the stria terminalis, dACC = dorsal anterior cingulate cortex, PAG = periaqueductal gray, thalamus, vmPFC = ventral medial prefrontal cortex, vStriatum = ventral striatum. We hypothesized that the aInsula, dACC, PAG, and thalamus show sensitivity to both reward and threat. Additionally, we hypothesized that the amygdala and BNST are predominantly sensitive to threat, while the vmPFC and vStriatum are predominantly sensitive to reward. Furthermore, we expected that the dACC and vmPFC are involved in the integration of reward and threat.

To gain global insight into the neural activation patterns probed by the task, independent of the level of reward, the level of threat, and the decision, we first report the results of the whole-brain voxel-wise analysis contrasting neural activity during the *decision phase* against the baseline (i.e., the intertrial interval).

Bayesian Multivariate Multilevel (BMM) fMRI analysis: effects of reward, threat, and decision

To investigate the effects of reward, threat, decision, and their interactions on neural activity within our regions of interest, we leveraged Bayesian Multivariate Multilevel (BMM) analyses. Particularly for intricate designs, BMM analyses surpass conventional MRI analyses by effectively managing data dependency and unbalanced data, leading to increased accuracy (Chen et al., 2019a, 2019b). We expected unbalanced data due to specific task conditions in which minimal within-subject variation can exist for the decision (approach vs avoid). Given that conducting BMM analyses on whole-brain voxel-wise level is not computationally feasible, we performed the BMM analyses on our regions of interest. In line with our preregistration, we also conducted two additional whole-brain voxel-wise analyses: one parametric modulation

analysis focussing on stimulus effects (i.e., the effect of reward/threat) and one general linear model (GLM) analysis focussing on response effects (i.e., the effect of the decision to approach or avoid). However, these additional analyses partially overlap with the BMM analyses, and the BMM analyses are more suitable for capturing higher-order interactions. Therefore, we focus on the BMM analyses, while further voxel-wise model specifications and results are provided at: https://osf.io/hbjp5.

Subject-level analysis

We employed subject-level models using SPM12 (Wellcome Trust Centre for Neuroimaging, London, UK). For each trial, we fitted one regressor for the *decision phase* (i.e., from trial onset until the response) and one regressor for the *outcome anticipation phase* (i.e., from response until the outcome). Additionally, we added regressors for each type of outcome (positive, negative, neutral) and motion regressors, leading to 190 regressors in total. For each trial, we contrasted the regressor of each phase against the regressors of the corresponding phase in all other trials. Finally, trial-by-trial mean betas for each phase were extracted for each ROI using the MarsBaR toolbox (Brett et al., 2002).

Group-level analysis

For each phase, we employed a Bayesian Multivariate Multilevel (BMM) analysis where we used the trial-by-trial betas of our ROIs as dependent variables. For full model specifications, see equation (2) below. Other model specifications were as described in the section 'Bayesian multilevel analyses (general)' above.

$$B_{aInsula}, B_{AMY}, B_{BNST}, B_{dACC},, B_{PAG}, B_{Thalamus}, B_{vStriatum}, B_{VMPFC} \sim \quad (2)$$
$$Reward * Threat * Decision + (1 + Reward * Threat * Decision \mid Subject)$$

Betas and posterior credible intervals of all main effects, interaction effects, and post-hoc comparisons are provided at: https://osf.io/hbjp5.

RESULTS

Avoidance behaviour

As expected, participants avoided significantly more with decreasing reward levels (*B* = -2.01, 99.9% CI [-3.49, -0.74]) and increasing threat levels (*B* = 1.79, 99.9% CI [0.86, 2.75], see Figure 3). In low threat conditions, the effect of reward appears to be less pronounced, as participants typically approach, while in high reward conditions, participants tend to approach regardless of threat. However, this was not reflected in a significant interaction between reward and threat on avoidance (*B* = -.01, 90% CI [-0.19, 0.15]).

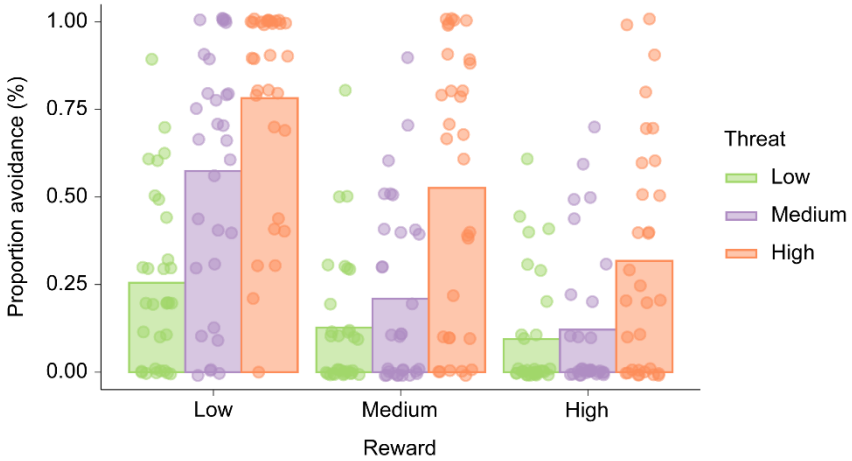

Figure 3. Overview task effects on avoidance behaviour. The bars represent the mean proportion avoidance as function of reward and threat level, overlaid with individual data points to illustrate variance between participants. Results showed the hypothesized opposing influences of reward and threat on avoidance.

fMRI: decision phase

Whole-brain voxel-wise analysis: decision phase vs baseline

Initial whole-brain voxel-wise analyses confirmed global activation across regions of interest hypothesized to be associated with weighing of reward and threat (aInsula, amygdala, BNST, dACC, PAG, thalamus, and vStriatum) when making approach-avoidance decisions (vs baseline; see Figure 4). Subsequently, to capture the weighing of rewards and threats for approach and avoidance decisions for each region of interest, we employed Bayesian Multivariate Multilevel (BMM) analyses.

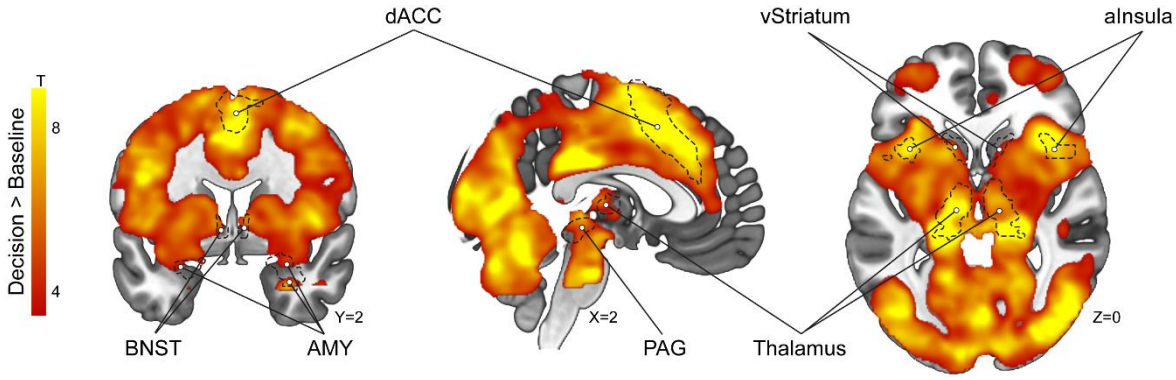

Figure 4. Whole-brain fMRI results demonstrating widespread activations during approach-avoidance decision-making (contrast: decision phase vs baseline). For illustrative purposes, images are shown at a threshold of $p<.001$ uncorrected. All marked regions of interests reach significance after correction for multiple comparisons ($p_{FWE}<.05$). aInsula = anterior insula, AMY = amygdala, BNST = bed nucleus of the stria terminalis, dACC = dorsal anterior cingulate cortex, PAG = periaqueductal gray, vStriatum = ventral striatum.

Bayesian Multivariate Multilevel fMRI analysis: reward, threat, and decision effects

First, we investigated the effects of reward, threat, decision, and their interactions on BOLD activity within our ROIs during the *decision phase*, i.e., prior to indicating approach-avoidance decisions (see Figure 5). We found that BOLD activity in the bed nucleus of the stria terminalis (BNST), periaqueductal gray (PAG), and ventral striatum increased as a function of reward, whereas BOLD activity in the dorsal anterior cingulate (dACC) increased as a function of threat. We did not find significant differences in overall BOLD activity between approach and avoidance decisions, nor significant interactions between reward and threat for any ROIs independent of decision (all 90% credible intervals overlapping with 0).

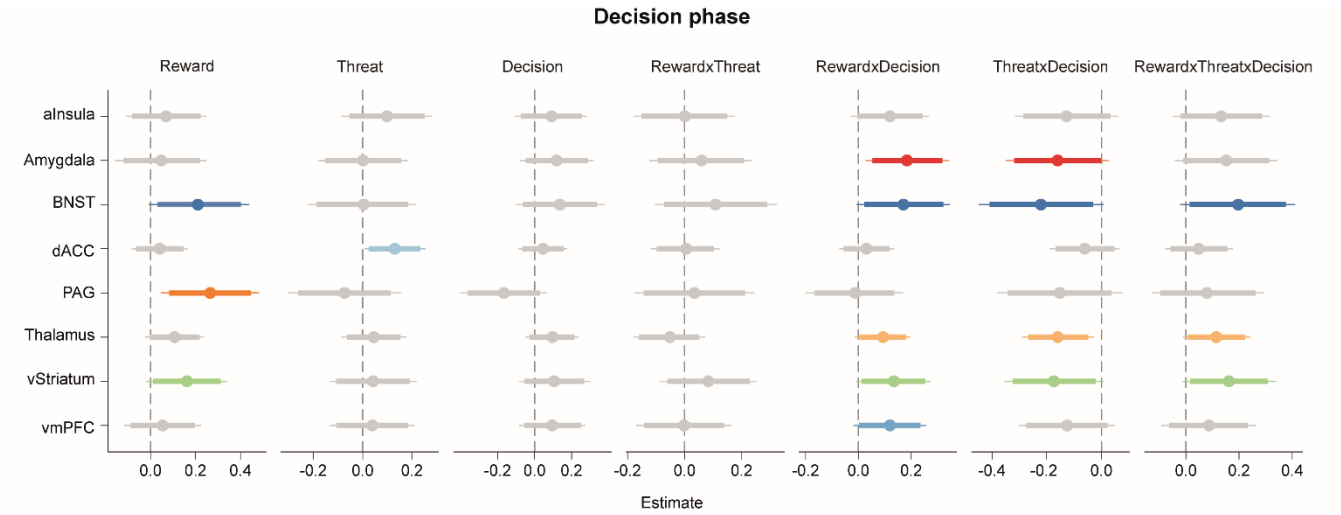

Figure 5. Posterior estimates and credible intervals for task-related activations in the regions of interest during the *decision phase*. This figure illustrates the posterior estimates (dots) with respect to the null (vertical dashed line). Bold lines represent 90% posterior credible intervals, while thin lines represent 95% posterior credible intervals. Significant effects, defined as ≥90% posterior credible intervals non-overlapping with zero, are highlighted in color. aInsula = anterior insula, BNST = bed nucleus of the stria terminalis, dACC = dorsal anterior cingulate cortex, PAG = periaqueductal gray, vmPFC = ventral medial prefrontal cortex, vStriatum = ventral striatum.

More importantly, we discovered that in several regions, the effect of reward and threat on BOLD activity differed between subsequent approach and avoidance decisions. Specifically, both the amygdala and vmPFC exhibited stronger BOLD activity with increasing reward preceding approach, but not avoidance decisions (reward x decision; see Figure 6A), in line with the idea that activity in these regions may drive approach reponses with increasing reward. Moreover, stronger BOLD activity was observed in the amygdala in response to increasing threat for avoidance relative to approach decisions (threat x decision; see Figure 6B), thus suggestive of a dual role for the amygdala in processing both rewards and threats. Interestingly, in addition to these two-way interactions, BOLD activity in the BNST, thalamus and ventral striatum exhibited a pattern suggesting that the integration of reward and threat differed for approach and avoidance decisions (reward x threat x decision; see Figure 6C). Specifically, when participants decided to avoid in low reward conditions, BOLD activity in the thalamus and ventral striatum was stronger with increasing threat. In contrast, prior to

indicating approach decisions in low reward conditions, BOLD activity in the BNST and ventral striatum was decreased with increasing threat. Conversely, no differences in threat reactivity between approach and avoidance decisions were found when reward was high and the impact of threat on decisions much smaller (see Figure 3).

In conclusion, our findings reveal that BOLD activity as a function of reward and threat preceding approach-avoidance decisions varied depending on the subsequent decision. Interestingly and contrary to theoretical predictions, several subcortical regions exhibited a pattern suggesting an integrative role.

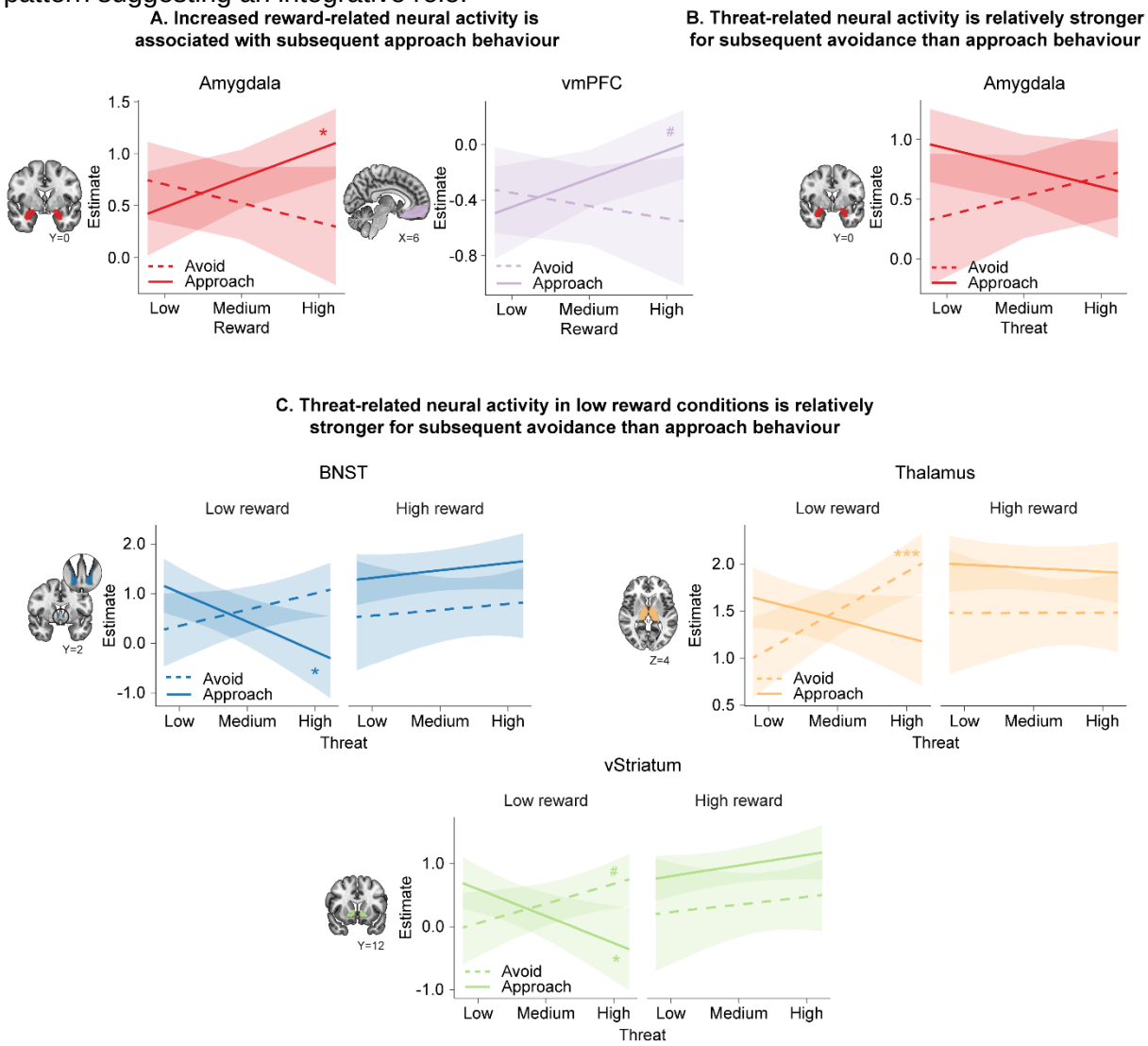

Figure 6. Effects of reward and threat on neural activity during approach-avoidance decision-making. The figure presents marginal effects plots for interactions between reward, threat, and decision in the *decision phase*. These plots depict seperately for approach (solid lines) and avoidance (dashed lines): **(A)** the effect of *reward*, **(B)** the effect of *threat*, and **(C)** the *interaction between reward and threat*

across all regions of interest where these interactions were observed. For each region of interst, only the highest-order interaction is plotted as it conveys most information. #≥90%, *≥95%, **≥99%, or ***≥99.9% posterior credible intervals non-overlapping with zero. vmPFC = ventomedial prefrontal cortex, BNST = bed nucleus of the stria terminalis, vStriatum = ventral striatum.

fMRI: outcome anticipation phase

Bayesian Multivariate Multilevel fMRI analysis: reward, threat, and decision effects

Recent research suggests involvement of specific brain regions may depend on the specific stage of the approach-avoidance decision-making process. Therefore, we subsequently probed the contribution of our ROIs at the stage following approach-avoidance decisions, when participants were passively anticipating the outcome. During this *outcome anticipation phase*, BOLD activity in the amygdala, BNST, PAG, and thalamus was more pronounced following approach decisions compared to avoidance decisions (see Figure 7). Given the higher likelihood of receiving a threatening outcome with approach decisions, this finding supports the hypothesized involvement of these regions in anxious anticipation. In line with this, we observed stronger BOLD activity in the aInsula and PAG with increasing threat. We did not find any significant main effects of reward nor interactions between reward and threat in any ROI (all 90% credible intervals overlapping with 0).

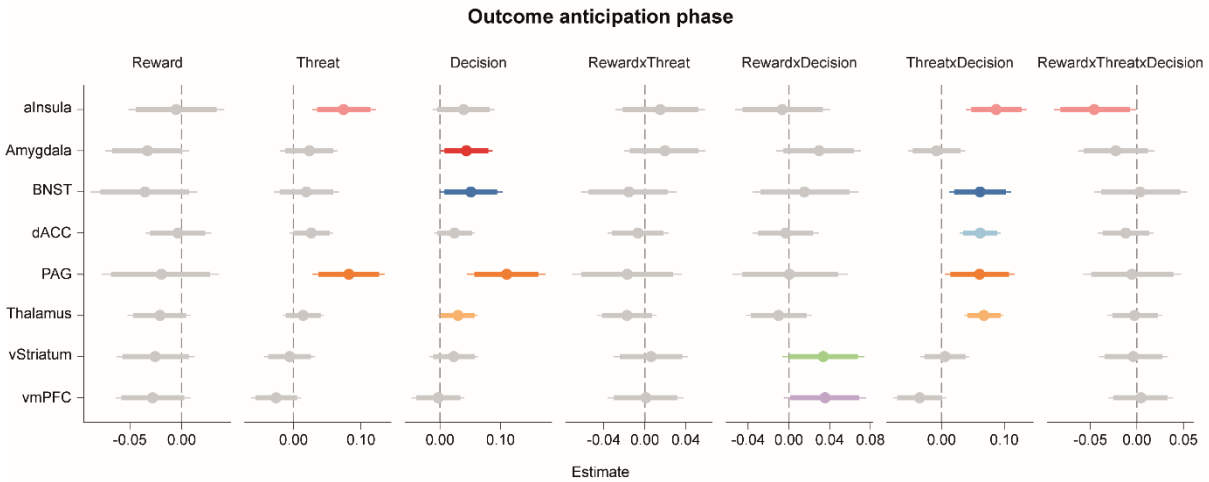

Figure 7. Posterior estimates and credible intervals for task-related activations in the regions of interest during the *outcome anticipation phase*. This figure illustrates the posterior estimates (dots) with respect to the null (vertical dashed line). Bold lines represent 90% posterior credible intervals, while thin lines represent 95% posterior credible intervals. Significant effects, defined as ≥90% posterior

credible intervals non-overlapping with zero, are highlighted in color. aInsula = anterior insula, BNST = bed nucleus of the stria terminalis, dACC = dorsal anterior cingulate cortex, PAG = periaqueductal gray, vmPFC = ventral medial prefrontal cortex, vStriatum = ventral striatum.

Interestingly, in several regions, the influence of reward and threat on the BOLD response during the outcome anticipation phase depended on the preceding decision. Following avoidance decisions, BOLD activity within the vStriatum and vmPFC significantly decreased with increasing reward, suggesting downregulation of reward-related activity when receiving rewards is unlikely. Conversely, no such effects were oberved following approach decisions (reward x decision; see Figure 8A). Furthermore, we found that following avoidance decisions, BOLD activity in the thalamus decreased with increasing threat. In contrast, following approach decisions, when the risk of receiving electrical stimulation was high, BOLD activity in the aInsula, BNST, dACC, PAG, and thalamus increased with increasing threat (threat x decision; see Figure 8B). This finding further aligns with the presumed role of these regions in anticipating impending threats. Notably, there was integration of reward and threat in the aInsula, exhibiting variations between approach and avoidance decisions (reward x threat x decision; see Figure 8C). This interaction was driven by the fact that while anticipating the outcome of avoidance decisions (low risk), BOLD activity in the aInsula was marginally decreased as a function of threat in low reward conditions. In contrast, while anticipating the outcome of approach decisions (high risk), BOLD activity in the aInsula increased as a function of threat in low reward conditions. Thus, the pattern of BOLD activity in the aInsula was similar to patterns observed in other threat anticipation regions. However, it was the only region that exclusively exhibited this pattern when reward was low.

In conclusion, following avoidance decisions, regions in the reward network tracked diminishing reward expectations, while upon approach decisions, regions from the salience network tracked threat prospects, with the aInsula only doing so when reward was low.

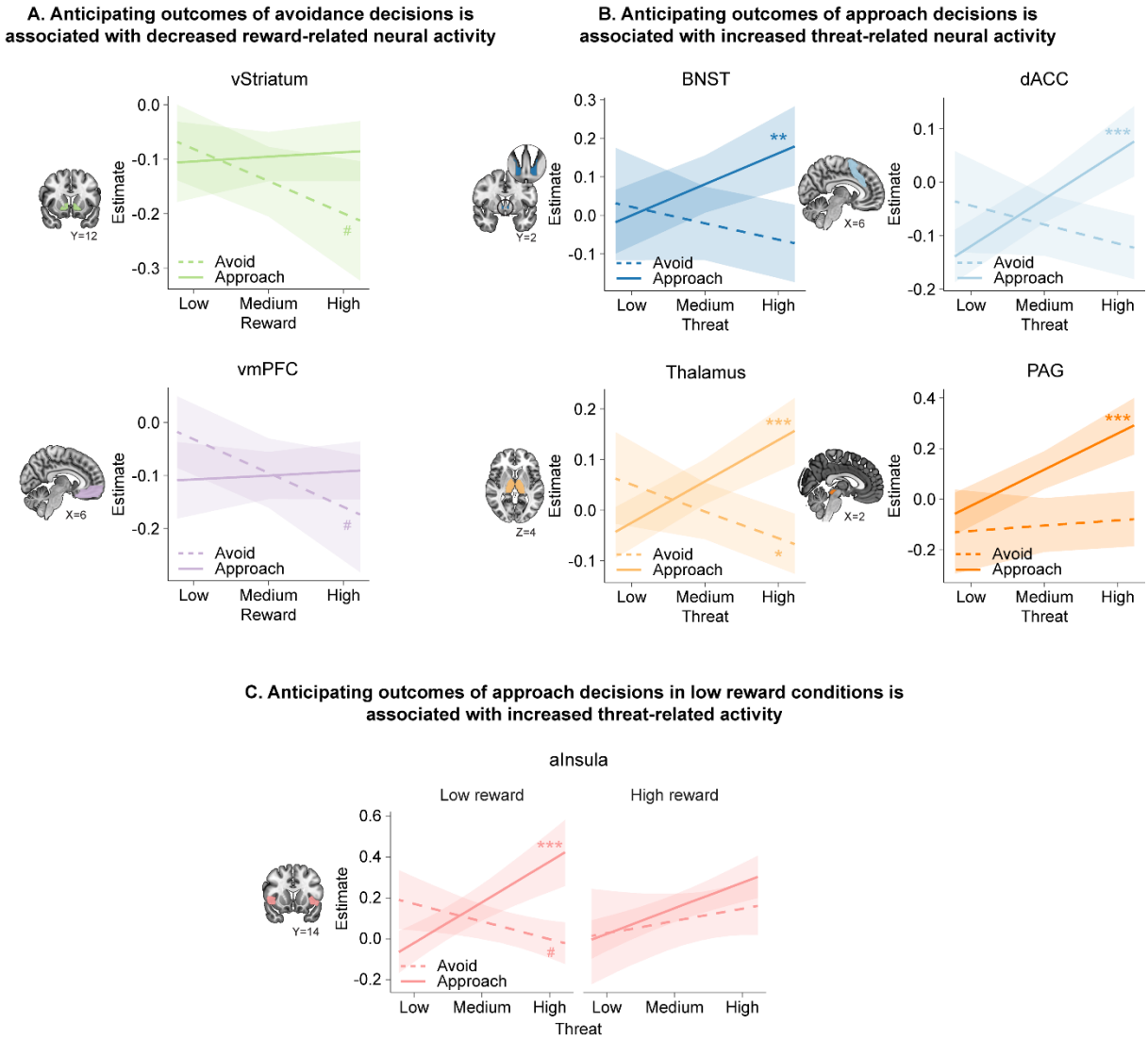

Figure 8. Effects of reward and threat on neural activity during anticipation of the outcome of approach-avoidance decisions. The figure presents marginal effects plots for interactions between reward, threat, and decision in the *outcome anticipation phase*. These plots depict seperately for approach (solid lines) and avoidance (dashed lines): **(A)** the effect of *reward*, **(B)** the effect of *threat*, and **(C)** the *interaction between reward and threat* across all regions of interest where these interactions were observed. For each region of interst, only the highest-order interaction is plotted as it conveys most information. #≥90%, *≥95%, **≥99%, or ***≥99.9% posterior credible intervals non-overlapping with zero. vStriatum = ventral striatum, vmPFC = ventromedial prefrontal cortex, BNST = bed nucleus of the stria terminalis, dACC = dorsal anterior cingulate cortex, PAG = periaqueductal gray, aInsula = anterior insula.

DISCUSSION

In this study, we investigated how the decision to approach or avoid may arise of distributed processing and integration of reward and threat information throughout the brain. We aimed to provide a better understanding of the neural dynamics governing approach-avoidance decisions by 1) investigating whether the decision to approach or avoid is preceded by parallel and/or integrated neural processing of reward and threat across brain regions previously implicated in approach-avoidance decision-making and 2) evaluated how such processing and integration evolve over time following approach-avoidance decisions during outcome anticipation. Our preregistered Bayesian Multivariate Multilevel (BMM) analyses on fMRI data revealed two key findings. First, in contrast to the notion of *parallel processing* of reward and threat in subcortical regions traditionally associated predominantly with either reward (vStriatum, vmPFC) or threat (amygdala, BNST) processing, we found evidence for *dual* and *integrated processing*. Specifically, there was *dual processing* of reward and threat information in the amygdala and evidence for *integration* in other subcortical regions, including the vStriatum, thalamus, and BNST. Critically, the weighing of reward and threat in these regions varied as a function of the subsequent decision to approach or avoid. Second, after indicating the decision to approach or avoid, we observed that the hypothesized regions associated with reward (vmPFC, vStriatum) and threat (BNST) processing, as well as the salience network (dACC, thalamus, PAG) were tracking reward and threat outcome expectations in accordance with previous theories. Together, these findings illuminate neural dynamics of approach-avoidance decision-making and suggest distributed subcortical integration of reward and threat as a potential driver of subsequent approach-avoidance decisions. In contrast, following the decision to approach or avoid, there is separate tracking of reward and threat outcome expectations by dedicated neural circuits. These neural circuits play a role in preparing for the anticipated consequences of the decision.

In accordance with prior research, we found that when making approach-avoidance decisions, individuals balance potential rewards and threats against each other (Talmi et al., 2009; Basten et al., 2010; Park et al., 2011; Aupperle et al., 2015; Schlund et al., 2016;

Hulsman et al., 2021a, 2024; Klaassen et al., 2021; Moughrabi et al., 2022). Subsequently, we employed Bayesian Multivariate Multilevel (BMM) analyses to delve deeper into the specific contributions of regions traditionally associated with reward and threat processing to approach-avoidance decision-making under these mixed outcome prospects. Notably, prior to indicating approach-avoidance decisions, distinct patterns of neural responding emerged. These patterns deviated from conventional perspectives, which primarily propose isolated reward and threat processing in subcortical regions, followed by the integration of reward and threat in cortical regions such as the ACC or vmPFC (Yacubian et al., 2006; Talmi et al., 2009; Basten et al., 2010; Park et al., 2011; Azab and Hayden, 2020; Livermore et al., 2021). Instead, our findings suggest that the decision to approach or avoid is supported by partially overlapping brain regions responding to both reward and threat information. Specifically, the amygdala, BNST, thalamus, and vStriatum showed a pattern of increasing neural activity as function of threat prior to indicating avoidance as compared to approach decisions. In contrast, the vmPFC uniquely displayed a reward-by-decision effect without being moderated by threat, consistent with its hypothesized role in reward valuation (Talmi et al., 2009; Aupperle and Paulus, 2010; Basten et al., 2010; Bartra et al., 2013) and subsequent approach decisions (Pedersen et al., 2021). The convergence of brain regions engaged in processing both reward and threat corresponds with recent findings demonstrating that the BNST, vStriatum, and PAG respond to both reward and threat information (Murty et al., 2023) and that conflict between approach and avoidance tendencies is represented at the level of the vStriatum (Ironside et al., 2020). Additionally, converging findings have shown that the amygdala responds to both aversive and appetitive stimuli (Baxter and Murray, 2002; O'Doherty, 2004; Schultz, 2006; Pessoa, 2010). These observations also align with long-standing reports in rodents (Gentry et al., 2016; Burgos-Robles et al., 2017; Hamel et al., 2017; Beyeler et al., 2018), collectively suggesting that the traditional notion of these regions responding primarily to either reward or threat is untenable. Nevertheless, it remains possible that depending on the context certain regions predominantly encode reward or threat information, as observed here, with vmPFC and PAG demonstrating sensitivity to reward and the dACC to threat. Tentatively, such signals could

serve as input for regions integrating both reward and threat inputs, such as the BNST, vStriatum, and thalamus. This perspective aligns with theories proposing that these regions, due to their connectivity profile, may serve as intermediaries between lower downstream subcortical and upstream cortical regions (Avery et al., 2014; Goode and Maren, 2017; De Groote and de Kerchove d'Exaerde, 2021; Hammack et al., 2021; Sieveritz and Raghavan, 2021), akin to striatal-thalamo-cortical loops in motor control (Pessoa, 2023).

The observed integration patterns of reward and threat notably diverge from prior human imaging research, which indicated such integration primarily in cortical regions such as the dACC, dlPFC, dmPFC, and inferior frontal gyrus (Basten et al., 2010; Park et al., 2011; Zorowitz et al., 2019; Moughrabi et al., 2022). Our findings of subcortical integration, therefore provide a new perspective although they do resonate with other previous non-human literature (Costa et al., 2016; Gentry et al., 2016; Burgos-Robles et al., 2017; Hamel et al., 2017). Furthermore, the observed increase in threat-related activity in the vStriatum, thalamus, and BNST preceding avoidance relative to approach under low reward, aligns with recent findings that increased threat representations in these regions during decision-making were linked to avoidance (Moughrabi et al., 2022). Behaviourally, the presence of high reward attenuated the impact of threat on subsequent decisions. This attenuation was also reflected in neural responses within the vStriatum, thalamus, and BNST. These findings further align with previous research outside the field of value-based decision making that demonstrate competition between reward and threat processing in various brain regions, including the BNST (Choi et al., 2014).

Finally, we demonstrated that neural patterns of processing and integration varied depending on the specific moment within the approach-avoidance conflict. After participants indicated the decision to approach or avoid and were anticipating the outcome of their decision, we found predominantly distinct tracking of reward or threat magnitude. Following approach decisions, we observed increased threat-related activity in the salience and threat network, encompassing the BNST, thalamus, dACC, and PAG, all of which have consistently been associated with threat anticipation (Mechias et al., 2010; Fullana et al., 2016; Klumpers et al.,

2017; Andrzejewski et al., 2019; Patrick et al., 2019). Interestingly, in the aInsula we only found increased threat-related activity following approach decisions when rewards were low. This aligns with previous research suggesting that the presence of reward can suppress the effect of threat in the aInsula (Cristofori et al., 2015). Conversely, following avoidance decisions we found decreased reward-related activity in the reward network, including the vStriatum and vmPFC. These findings appear to reflect decreased reward expectancies after avoidance decisions (Heekeren et al., 2007; Jia et al., 2016; Pujara et al., 2016; Rehbein et al., 2023).

Despite the implementation of a fast multiband-multiecho fMRI sequence (MB3ME3), our findings cannot fully reflect the temporal dynamics of approach-avoidance decisions due to the inherent limitations in the temporal resolution of fMRI. To further delineate the temporal dynamics of approach-avoidance decisions, employing methods with superior temporal resolution, such as MEG or EEG, are informative (Khemka et al., 2017; McFadyen et al., 2023). Another limitation for our study is a relatively small sample size (N=28 included in MRI analyses). However, our analyses were preregistered, and we employed BMM analyses to investigate neural responses, thereby minimizing the risk of false positives (Kajimura et al., 2023). Still, replication of our findings is desirable, particularly in clinical populations that show approach-avoidance deficits to gain further knowledge of how reward-threat balances across distinct regions may be disturbed (Ironside et al., 2020; Smith et al., 2021b, 2021a, 2023; McDermott et al., 2022).

In conclusion, our findings unveiled distributed cortico-subcortical processing and subcortical integration of reward and threat prior to the decision to approach or avoid. These findings suggest a departure from traditional, yet still widely professed, views that segregate brain regions as either predominantly reward-sensitive or threat-sensitive, and assign the integration of reward and threat primarily to cortical regions. Following approach-avoidance decisions, however, brain regions traditionally associated with reward and threat processing reflected reward and threat expectencies contingent on the decision that was made. These findings provide new insight into the unfolding neural dynamics of approach-avoidance decision-making.

References

Abivardi A, Khemka S, Bach DR (2020) Hippocampal Representation of Threat Features and Behavior in a Human Approach–Avoidance Conflict Anxiety Task. J Neurosci 40:6748–6758.

Alvarez EO, Ruarte MB (2001) Role of glutamate receptors in the nucleus accumbens on behavioural responses to novel conflictive and non-conflictive environments in the rat. Behav Brain Res 123:143–153.

American Psychiatric Association (2013) Diagnostic and statistical manual of mental disorders, 5th ed. Washington, DC. Available at: https://doi.org/10.1176/appi.books.9780890425596.

Andrzejewski JA, Greenberg T, Carlson JM (2019) Neural correlates of aversive anticipation: An activation likelihood estimate meta-analysis across multiple sensory modalities. Cogn Affect Behav Neurosci 19:1379–1390.

Aupperle RL, Melrose AJ, Francisco A, Paulus MP, Stein MB (2015) Neural substrates of approach-avoidance conflict decision-making. Hum Brain Mapp 36:449–462.

Aupperle RL, Paulus MP (2010) Neural systems underlying approach and avoidance in anxiety disorders. Dialogues Clin Neurosci 12:517–531.

Avery SN, Clauss JA, Winder DG, Woodward N, Heckers S, Blackford JU (2014) BNST neurocircuitry in humans. NeuroImage 91:311–323.

Azab H, Hayden B (2020) Partial integration of the components of value in anterior cingulate cortex. Behav Neurosci 134:296–308.

Bartra O, McGuire JT, Kable JW (2013) The valuation system: A coordinate-based meta-analysis of BOLD fMRI experiments examining neural correlates of subjective value. NeuroImage 76:412–427.

Basten U, Biele G, Heekeren HR, Fiebach CJ (2010) How the brain integrates costs and benefits during decision making. Proc Natl Acad Sci 107:21767–21772.

Baxter MG, Murray EA (2002) The amygdala and reward. Nat Rev Neurosci 3:563–573.

Beaufour CC, Le Bihan C, Hamon M, Thiébot MH (2001) Extracellular serotonin is enhanced in the striatum, but not in the dorsal hippocampus or prefrontal cortex, in rats subjected to an operant conflict procedure. Behav Neurosci 115:125–137.

Beyeler A, Chang C-J, Silvestre M, Lévêque C, Namburi P, Wildes CP, Tye KM (2018) Organization of Valence-Encoding and Projection-Defined Neurons in the Basolateral Amygdala. Cell Rep 22:905–918.

Brett M, Anton J-L, Valabregue R, Poline J-B (2002) Region of interest analysis using an SPM toolbox [abstract].

Burgos-Robles A, Kimchi EY, Izadmehr EM, Porzenheim MJ, Ramos-Guasp WA, Nieh EH, Felix-Ortiz AC, Namburi P, Leppla CA, Presbrey KN, Anandalingam KK, Pagan-Rivera PA, Anahtar M, Beyeler A, Tye KM (2017) Amygdala inputs to prefrontal cortex guide behavior amid conflicting cues of reward and punishment. Nat Neurosci 20:824–835.

Bürkner P-C (2013) brms : An R Package for Bayesian Multilevel Models using Stan. J Stat Softw 80:1–28.

Carpenter B, Gelman A, Hoffman MD, Lee D, Goodrich B, Betancourt M, Brubaker MA, Li P, Riddell A (2017) Stan : A Probabilistic Programming Language. J Stat Softw 76.

Chen G, Paul PB, Zhihao AT, Lijun L, Glen DR, Kinnison J, Cox RW, Pessoa L (2019a) An integrative Bayesian approach to matrix-based analysis in neuroimaging. Hum Brain Mapp:4072–4090.

Chen G, Xiao Y, Taylor PA, Rajendra JK, Riggins T, Geng F, Redcay E, Cox RW (2019b) Handling Multiplicity in Neuroimaging Through Bayesian Lenses with Multilevel Modeling. Neuroinformatics 17:515–545.

Ch'ng S, Fu J, Brown RM, McDougall SJ, Lawrence AJ (2018) The intersection of stress and reward: BNST modulation of aversive and appetitive states. Prog Neuropsychopharmacol Biol Psychiatry 87:108–125.

Choi JM, Padmala S, Spechler P, Pessoa L (2014) Pervasive competition between threat and reward in the brain. Soc Cogn Affect Neurosci 9:737–750.

Cohen AD, Nencka AS, Wang Y (2018) Multiband multi-echo simultaneous ASL/ BOLD for task-induced functional MRI. PLoS ONE 13:1–21.

Corr PJ (2013) Approach and Avoidance Behaviour: Multiple Systems and their Interactions. Emot Rev 5:285–290.

Costa VD, Dal Monte O, Lucas DR, Murray EA, Averbeck BB (2016) Amygdala and Ventral Striatum Make Distinct Contributions to Reinforcement Learning. Neuron 92:505–517.

Cristofori I, Harquel S, Isnard J, Mauguière F, Sirigu A (2015) Monetary reward suppresses anterior insula activity during social pain. Soc Cogn Affect Neurosci 10:1668–1676.

De Groote A, de Kerchove d'Exaerde A (2021) Thalamo-Nucleus Accumbens Projections in Motivated Behaviors and Addiction. Front Syst Neurosci 15:711350.

Duque-Wilckens N, Steinman MQ, Busnelli M, Chini B, Yokoyama S, Pham M, Laredo SA, Hao R, Perkeybile AM, Minie VA, Tan PB, Bales KL, Trainor BC (2018) Oxytocin Receptors in the Anteromedial Bed Nucleus of the Stria Terminalis Promote Stress-Induced Social Avoidance in Female California Mice. Biol Psychiatry 83:203–213.

Engelke DS, Zhang XO, O'Malley JJ, Fernandez-Leon JA, Li S, Kirouac GJ, Beierlein M, Do-Monte FH (2021) A hypothalamic-thalamostriatal circuit that controls approach-avoidance conflict in rats. Nat Commun 12:2517.

Fazal Z, Gomez DEP, Llera A, Marques JPRF, Beck T, Poser BA, Norris DG (2023) A comparison of multiband and multiband multiecho gradient-echo EPI for task fMRI at 3 T. Hum Brain Mapp 44:82–93.

Fullana MA, Harrison BJ, Vervliet B, Cardoner N, Radua J (2016) Neural signatures of human fear conditioning: an updated and extended meta-analysis of fMRI studies. Mol Psychiatry 21:500–508.

Gentry RN, Lee B, Roesch MR (2016) Phasic dopamine release in the rat nucleus accumbens predicts approach and avoidance performance. Nat Commun 7:13154.

Giardino WJ, Eban-Rothschild A, Christoffel DJ, Li S-B, Malenka RC, de Lecea L (2018) Parallel circuits from the bed nuclei of stria terminalis to the lateral hypothalamus drive opposing emotional states. Nat Neurosci 21:1084–1095.

Goode TD, Maren S (2017) Role of the bed nucleus of the stria terminalis in aversive learning and memory. Learn Mem 24:480–491.

Hamel L, Thangarasa T, Samadi O, Ito R (2017) Caudal Nucleus Accumbens Core Is Critical in the Regulation of Cue-Elicited Approach-Avoidance Decisions. eNeuro 4.

Hammack SE, Braas KM, May V (2021) Chemoarchitecture of the BNST: neurophenotypic diversity and function. Handb Clin Neurol 179:385–402.

Heekeren HR, Wartenburger I, Marschner A, Mell T, Villringer A, Reischies FM (2007) Role of ventral striatum in reward-based decision making. NeuroReport 18:951.

Hu P, Liu J, Maita I, Kwok C, Gu E, Gergues MM, Kelada F, Phan M, Zhou J-N, Swaab DF, Pang ZP, Lucassen PJ, Roepke TA, Samuels BA (2020) Chronic Stress Induces Maladaptive Behaviors by Activating Corticotropin-Releasing Hormone Signaling in the Mouse Oval Bed Nucleus of the Stria Terminalis. J Neurosci Off J Soc Neurosci 40:2519–2537.

Hulsman AM, Kaldewaij R, Hashemi MM, Zhang W, Koch SBJ, Figner B, Roelofs K, Klumpers F (2021a) Individual differences in costly fearful avoidance and the relation to psychophysiology. Behav Res Ther 137:103788.

Hulsman AM, Klaassen FH, Roelofs K, Klumpers F (2021b) Neural Mechanisms Underlying Fearful Avoidance Behaviour. Available at: osf.io/7sm9k.

Hulsman AM, Terburg D, Roelofs K, Klumpers F (2021c) Chapter 28 Roles of the bed nucleus of the stria terminalis and amygdala in fear reactions (Swaab DF, Kreier F, Lucassen PJ, Salehi A, Buijs R, eds).

Hulsman AM, van de Pavert I, Roelofs K, Klumpers F (2024) Tackling Costly Fearful Avoidance Using Pavlovian Counterconditioning. Behav Ther 55:361–375.

Hur J, Smith JF, DeYoung KA, Anderson AS, Kuang J, Kim HC, Tillman RM, Kuhn M, Fox AS, Shackman AJ (2020) Anxiety and the neurobiology of temporally uncertain threat anticipation. J Neurosci 40:7949–7964.

Ironside M, Amemori K, McGrath CL, Pedersen ML, Kang MS, Amemori S, Frank MJ, Graybiel AM, Pizzagalli DA (2020) Approach-Avoidance Conflict in Major Depressive

Disorder: Congruent Neural Findings in Humans and Nonhuman Primates. Biol Psychiatry 87:399–408.

Jia T et al. (2016) Neural basis of reward anticipation and its genetic determinants. Proc Natl Acad Sci 113:3879–3884.

Kajimura S, Hoshino T, Murayama K (2023) Stimulus-specific random effects inflate false-positive classification accuracy in multivariate-voxel-pattern-analysis: A solution with generalized mixed-effects modelling. NeuroImage 269:119901.

Khemka S, Barnes G, Dolan RJ, Bach DR (2017) Dissecting the Function of Hippocampal Oscillations in a Human Anxiety Model. J Neurosci 37:6869–6876.

Klaassen FH, Held L, Figner B, O'Reilly JX, Klumpers F, de Voogd LD, Roelofs K (2021) Defensive freezing and its relation to approach–avoidance decision-making under threat. Sci Rep 11:1–12.

Klumpers F, Kroes MCW, Baas J, Fernández G (2017) How human amygdala and bed nucleus of the stria terminalis may drive distinct defensive responses. J Neurosci 37:3830–16.

Klumpers F, Raemaekers MAHL, Ruigrok ANV, Hermans EJ, Kenemans JL, Baas JMP (2010) Prefrontal mechanisms of fear reduction after threat offset. Biol Psychiatry 68:1031–1038.

Kruschke JK (2014) Doing Bayesian data analysis: A tutorial with R, JAGS, and Stan. Academic Press.

Lenth R, Singmann H, Love J, Buerkner P, Herve M (2018) Emmeans. R Package Version 115-15 34:216–221.

Livermore JJA, Klaassen FH, Bramson B, Hulsman AM, Meijer SW, Held L, Klumpers F, de Voogd LD, Roelofs K (2021) Approach-Avoidance Decisions Under Threat: The Role of Autonomic Psychophysiological States. Front Neurosci 15.

Lojowska M, Gladwin TE, Hermans EJ, Roelofs K (2015) Freezing promotes perception of coarse visual features. J Exp Psychol Gen 144:1080–1088.

Makowski D, Ben-Shachar M, Lüdecke D (2019) bayestestR: Describing Effects and their Uncertainty, Existence and Significance within the Bayesian Framework. J Open Source Softw 4:1541.

McDermott TJ, Berg H, Touthang J, Akeman E, Cannon MJ, Santiago J, Cosgrove KT, Clausen AN, Kirlic N, Smith R, Craske MG, Abelson JL, Paulus MP, Aupperle RL (2022) Striatal reactivity during emotion and reward relates to approach–avoidance conflict behaviour and is altered in adults with anxiety or depression. J Psychiatry Neurosci 47:E311–E322.

McFadyen J, Liu Y, Dolan RJ (2023) Differential replay of reward and punishment paths predicts approach and avoidance. Nat Neurosci 26:627–637.

Mechias M-L, Etkin A, Kalisch R (2010) A meta-analysis of instructed fear studies: Implications for conscious appraisal of threat. NeuroImage 49:1760–1768.

Miller SM, Marcotulli D, Shen A, Zweifel LS (2019) Divergent medial amygdala projections regulate approach-avoidance conflict behavior. Nat Neurosci 22.

Moughrabi N, Botsford C, Gruichich TS, Azar A, Heilicher M, Hiser J, Crombie KM, Dunsmoor JE, Stowe Z, Cisler JM (2022) Large-scale neural network computations and multivariate representations during approach-avoidance conflict decision-making. NeuroImage 264:119709.

Murty DVPS, Song S, Surampudi SG, Pessoa L (2023) Threat and Reward Imminence Processing in the Human Brain. J Neurosci 43:2973–2987.

O'Doherty JP (2004) Reward representations and reward-related learning in the human brain: insights from neuroimaging. Curr Opin Neurobiol 14:769–776.

Park SQ, Kahnt T, Rieskamp J, Heekeren HR (2011) Neurobiology of Value Integration: When Value Impacts Valuation. J Neurosci 31:9307–9314.

Patrick F, Kempton MJ, Marwood L, Williams SCR, Young AH, Perkins AM (2019) Brain activation during human defensive behaviour: A systematic review and preliminary meta-analysis. Neurosci Biobehav Rev 98:71–84.

Pedersen ML, Ironside M, Amemori KI, McGrath CL, Kang MS, Graybiel AM, Pizzagalli DA, Frank MJ (2021) Computational phenotyping of brain-behavior dynamics underlying approach-avoidance conflict in major depressive disorder. PLoS Comput Biol 17:1–21.

Pessoa L (2010) Emotion and cognition and the amygdala: From “what is it?” to “what’s to be done?” Neuropsychologia 48:3416–3429.

Pessoa L (2023) How many brain regions are needed to elucidate the neural bases of fear and anxiety? Neurosci Biobehav Rev 146:105039.

Piray P, den Ouden HEM, van der Schaaf ME, Toni I, Cools R (2017) Dopaminergic Modulation of the Functional Ventrodorsal Architecture of the Human Striatum. Cereb Cortex 27:485–495.

Poser BA, Versluis MJ, Hoogduin JM, Norris DG (2006) BOLD contrast sensitivity enhancement and artifact reduction with multiecho EPI: Parallel-acquired inhomogeneity-desensitized fMRI. Magn Reson Med 55:1227–1235.

Pujara MS, Philippi CL, Motzkin JC, Baskaya MK, Koenigs M (2016) Ventromedial Prefrontal Cortex Damage Is Associated with Decreased Ventral Striatum Volume and Response to Reward. J Neurosci 36:5047–5054.

Rehbein MA, Kroker T, Winker C, Ziehfreund L, Reschke A, Bölte J, Wyczesany M, Roesmann K, Wessing I, Junghöfer M (2023) Non-invasive stimulation reveals ventromedial prefrontal cortex function in reward prediction and reward processing. Front Neurosci 17:1219029.

Rolls ET, Huang C-C, Lin C-P, Feng J, Joliot M (2020) Automated anatomical labelling atlas 3. NeuroImage 206:116189.

Schlund MW, Brewer AT, Magee SK, Richman DM, Solomon S, Ludlum MD, Dymond S (2016) The tipping point: Value differences and parallel dorsal-ventral frontal circuits gating human approach-avoidance behavior. NeuroImage 136:94–105.

Schultz W (2006) Behavioral Theories and the Neurophysiology of Reward. Annu Rev Psychol 57:87–115.

Shackman AJ, Fox AS (2016) Contributions of the Central Extended Amygdala to Fear and Anxiety. J Neurosci 36:8050–8063.

Shirer WR, Ryali S, Rykhlevskaia E, Menon V, Greicius MD (2012) Decoding Subject-Driven Cognitive States with Whole-Brain Connectivity Patterns. Cereb Cortex N Y NY 22:158–165.

Sieveritz B, Raghavan RT (2021) The Central Thalamus: Gatekeeper or Processing Hub? J Neurosci 41:4954–4956.

Smith R, Kirlic N, Stewart JL, Touthang J, Kuplicki R, Khalsa SS, Feinstein J, Paulus MP, Aupperle RL (2021a) Greater decision uncertainty characterizes a transdiagnostic patient sample during approach-avoidance conflict: a computational modelling approach. J Psychiatry Neurosci 46:E74–E87.

Smith R, Kirlic N, Stewart JL, Touthang J, Kuplicki R, McDermott TJ, Taylor S, Khalsa SS, Paulus MP, Aupperle RL (2021b) Long-term stability of computational parameters during approach-avoidance conflict in a transdiagnostic psychiatric patient sample. Sci Rep 11:1–13.

Smith R, Lavalley CA, Taylor S, Stewart JL, Khalsa SS, Berg H, Ironside M, Paulus MP, Aupperle R (2023) Elevated decision uncertainty and reduced avoidance drives in depression, anxiety and substance use disorders during approach–avoidance conflict: a replication study. J Psychiatry Neurosci 48:E217–E231.

Talmi D, Dayan P, Kiebel SJ, Frith CD, Dolan RJ (2009) How Humans Integrate the Prospects of Pain and Reward during Choice. J Neurosci 29:14617–14626.

Warlow SM, Naffziger EE, Berridge KC (2020) The central amygdala recruits mesocorticolimbic circuitry for pursuit of reward or pain. Nat Commun 11:2716.

Yacubian J, Gläscher J, Schroeder K, Sommer T, Braus DF, Büchel C (2006) Dissociable systems for gain- and loss-related value predictions and errors of prediction in the human brain. J Neurosci 26:9530–9537.

Zhou K, Xu H, Lu S, Jiang S, Hou G, Deng X, He M, Zhu Y (2022) Reward and aversion processing by input-defined parallel nucleus accumbens circuits in mice. Nat Commun 13:6244.

Zorowitz S, Rockhill AP, Ellard KK, Link KE, Herrington T, Pizzagalli DA, Widge AS, Deckersbach T, Dougherty DD (2019) The Neural Basis of Approach-Avoidance Conflict: A Model Based Analysis. eneuro 6:1–12.