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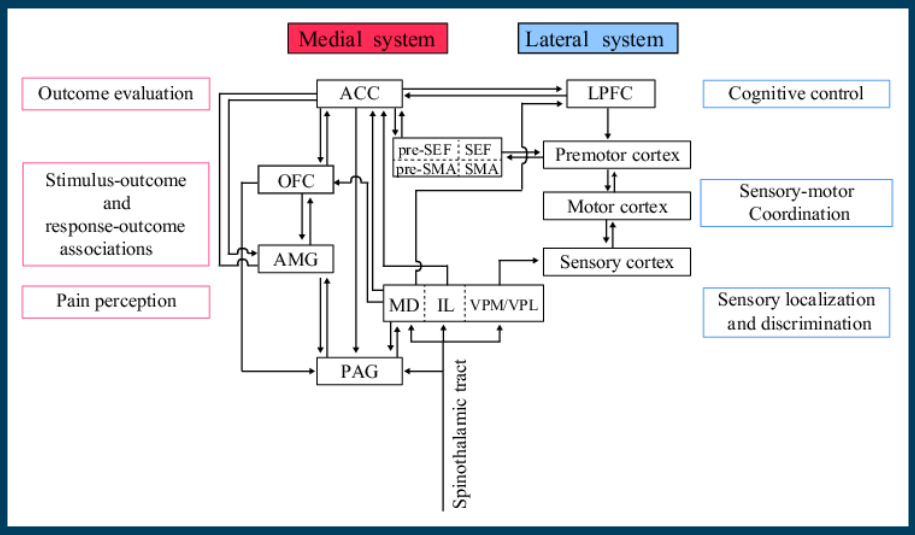

PUNISHMENT-BASED DECISION MAKING

Topic Editors
Jean-Claude Dreher, Ben Seymour and Philippe N. Tobler

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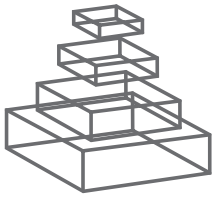

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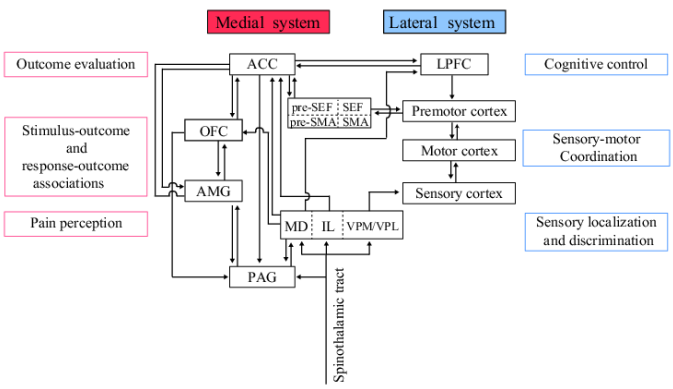
PUNISHMENT-BASED DECISION MAKING

Topic Editors:
Jean-Claude Dreher, CNRS, National Scientific Research Center, France
Ben Seymour, University of Cambridge, United Kingdom
Philippe N. Tobler, University of Zurich, Switzerland



Conceptual schema illustrating the functional dichotomy between the medial and lateral systems. The medial system includes the amygdala (AMG), periaqueductal gray (PAG), orbitofrontal cortex (OFC), and anterior cingulate cortex (ACC), and serves as a predictor and evaluator of behavioral outcomes. The lateral system receives multimodal sensory inputs and processes the signals to obtain physical information regarding the environment. Sensory information is transferred to the LPFC for cognitive decision-making and action planning. The ACC provides feedback information to the LPFC to implement behavioral adaptation based on outcome values. MD, mediodorsal nucleus of the thalamus; IL, intralaminar nucleus of the thalamus; VPM/VPL, ventral posteromedial nucleus/ventral posterolateral nucleus of the thalamus; SMA, supplementary motor area; pre-SMA, presupplementary motor area; LPFC, lateral prefrontal cortex.

Taken from: Kobayashi S (2012) Organization of neural systems for aversive information processing: pain, error, and punishment. *Front. Neurosci.* 6:136. doi: 10.3389/fnins.2012.00136

This e-book reports recent findings on the neural mechanisms underlying approach and avoidance behaviour in the face of rewards and punishments. This e-book aims to understand the nature of critical differences and asymmetries between the ways that appetitive and aversive outcomes are processed by the brain. A number of topics are covered, such as the development of economic additive and interactive models integrating costs and benefits into a single value, neuroimaging approaches of appetitive and aversive conditioning (eg. fear and pain conditioning), reward-punishment interactions, the roles of the amygdala, striatum, orbitofrontal cortex, anterior cingulate cortex and periacqueductal gray in pain and defensive behavior, the role of dopamine neurons in aversive conditioning, the interactions between serotonin and dopamine in punishment, pain and aversion… The neural bases of reward-punishment interactions are investigated with a variety of approaches and levels of analysis, from basic neural mechanisms and computational models of appetitive and aversive conditioning, to the system neuroscience level.

We anticipate that while some readers may read this Frontiers Research Topic from the first to the last chapter, other readers may read only one or more chapters at a time, and not necessarily in the order presented in this e-book. This is why we encouraged an organization of this volume whereby each chapter can stand alone, while making references to others and minimizing redundancies across the e-book.

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EDITORIAL
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Punishment-based decision making

Jean-Claude Dreher[1]*, Ben Seymour[2] and Philippe N. Tobler[3]

[1] *Reward and Decision Making Group, Centre de Neurosciences Cognitives, Centre National de la Recherche Scientifique, Lyon, France*
[2] *Center for Information and Neural Networks, National Institute for Information and Communications Technology, Osaka, Japan*
[3] *Laboratory for Social and Neural Systems Research, Department of Economics, University of Zurich, Zurich, Switzerland*
**Correspondence: dreher@isc.cnrs.fr*

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Keywords: punishment, reward, decision making, dopamine, serotonin

This Research Topic covers issues in psychology, behavioral economics, and cognitive neuroscience investigating the neural structures and mechanisms underlying approach, and avoidance behavior in the face of rewards and punishments. The objective is to understand the nature of critical differences and asymmetries between the ways that appetitive and aversive outcomes are processed by the brain. A number of topics are covered, such as the development of economic models integrating costs and benefits into a single value, neuroimaging approaches of appetitive and aversive conditioning, reward-punishment interactions, pain and defensive behavior, the role of dopamine neurons in aversive conditioning, and the interactions between serotonin and dopamine in punishment, pain, and aversion. The neural bases of reward-punishment interactions are of great interest to a broad readership because of the fundamental role of dopamine and serotonin in a number of motivational and decision processes, and because of their theoretical and clinical implications for understanding dysfunctions of these two systems. Findings in this research field are also important to basic neuroscientists interested in the computational processes of pain and aversive learning and cognitive psychologists working on conditioning/reinforcement. Punishment-based decision making and reward processing cover a wide range of topics and levels of analysis, from basic neural mechanisms and computational models of appetitive and aversive conditioning, to the system neuroscience level. The contributions to this Frontiers Research Topic in Decision Neuroscience are forward-looking assessments of the current and future issues faced by researchers.

RESEARCH ARTICLES

Porcelli et al. (2012) investigate how stress influences reward and punishment processing neural circuitry. They report results from a new fMRI study where participants were exposed to acute stress or a no stress control procedure and subsequently performed a fMRI paradigm where they received monetary rewards and punishments. Acute stress group participants' dorsal striatum and orbitofrontal cortex response demonstrated decreased sensitivity to monetary outcomes and a lack of differential activity. The reported findings provide insights into how neural circuits may process rewards and punishments associated with simple decisions under acutely stressful conditions.

In a second study, Singh and Khan (2012) studied the effect of reward and punishment sensitivity on long-term advantageous decisions in two variants of the Iowa gambling task (IGT). The results indicate that foresight in IGT decision making is sensitive to reward and punishment frames in an asymmetric manner. Moreover, variant, order, and instruction types had an effect on long-term decision making in the IGT.

In the third article, Rigoli et al. (2012) studied how aversive Pavlovian responses affect instrumental motor performance. Based on animal studies which have demonstrated that Pavlovian mechanisms can have maladaptive effects on instrumental performance, the authors report that Pavlovian responses influenced performance, and can also have maladaptive effects in humans. In particular, Pavlovian responses either impaired or increased performance depending on variables such as threat distance, task controllability, punishment history, amount of training and explicit punishment expectancy. Overall, these findings help to elucidate the mechanisms underlying the interaction between Pavlovian and instrumental-performance.

REVIEW ARTICLES

Barberini et al. (2012) focus on reviewing neural signals during and after learning in the amygdala and orbitofrontal cortex, two brain areas that process appetitive and aversive stimuli. They reveal a dynamic relationship between appetitive and aversive circuits which shifts as a function of learning. Furthermore, although appetitive and aversive circuits may often drive opposite behaviors, these circuits can also drive similar behaviors, such as enhanced arousal or attention. These data highlight the existing challenges to pinpoint how appetitive and aversive neural circuits interact to produce a range of behaviors.

In a review article, Kobayashi (2012) extends the previous mini-review in several ways. He presents the medial pain system, including the amygdala, periaqueductal gray (PAG), and anterior cingulate cortex (ACC), that signals pain and negative value. He reviews behavioral and physiological studies on the aversive system and proposes a conceptual framework for understanding the neural organization of the aversive avoidance system. According to this framework, it is possible to distinguish between a medial system including the amygdala-PAG-orbitofrontal cortex (OFC), and ACC, serving as a predictor and evaluator of behavioral outcomes, and a lateral system, which includes the lateral prefontal cortex and receives multimodal sensory inputs.

Wiech and Tracey (2013) review the relationship between pain and motivational states, providing an overview on behavioral and neuroimaging studies investigating motivational aspects of pain. They highlight insights into the modulation of pain through fear and social factors, summarize findings on the role of pain in fear conditioning, avoidance learning and goal conflicts and discuss

evidence on pain-related cognitive interference and motivational aspects of pain relief.

In a mini review, Ilango et al. (2012) examine the role of dopamine in response to aversive stimuli. The authors review data from electrophysiology, microdialysis and voltammetry describing dopamine changes in response to aversive stimuli and fearful events. For example, they show that dopamine neurons respond to aversive stimuli primarily with inhibition. They also describe the role of dopamine manipulations on signaled avoidance learning, which consists of learning the significance of a warning cue through Pavlovian associations and the execution of an instrumental avoidance response. They present a framework to understand the involvement of reward circuit in punishment based decisions.

In another paper, McCutcheon et al. (2012) review data indicating that Nucleus Accumbens (NAc) shell dopamine responses match the hedonic value of stimuli. They also present new data showing that oral infusion of sucrose suppresses instead of enhances NAc shell dopamine if the sucrose has been rendered aversive through previous pairing with malaise-inducing injection of lithium chloride. Sucrose infusions led to a suppression of dopamine with a similar magnitude and time course to intra-oral infusions of quinine solution. The results are discussed in the context of regional differences in dopamine signaling in the NAc.

Finally, Talmi and Pine (2012) review behavioral economic literature and describe models integrating costs and benefits into a single subjective value. They propose ways to assess these models beyond goodness of fit, such as how to model decisions between costs when reward is not on offer and whether these models predict changes in reward sensitivity when costs are added to outcomes. They also provide a selective review of relevant neurobiological work from a computational perspective, focusing on neuroimaging studies focusing on valuation mechanisms.

We anticipate that while some readers may read this Frontiers Research Topic from the first to the last chapter, other readers may read only one or more chapters at a time, and not necessarily in the order presented in this e-book. This is why we encouraged an organization of this volume whereby each chapter can stand alone, while making references to others and minimizing redundancies across the e-book.

Given the consistent acceleration of advances in the different approaches described in this Research Topic, we hope that you will enjoy these new stages of an exciting era in neuroscience research on the interactions between appetitive and aversive systems.

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Acute stress influences neural circuits of reward processing

Anthony J. Porcelli*[1]*, *Andrea H. Lewis*[2] *and *Mauricio R. Delgado*[2]

[1] *Department of Psychology, Marquette University, Milwaukee, WI, USA*
[2] *Department of Psychology, Rutgers University, Newark, NJ, USA*

Edited by:
Philippe N. Tobler, University of Zurich, Switzerland

Reviewed by:
Lars Schwabe, Ruhr-University Bochum, Germany
Sandra Cornelisse, University Medical Center Utrecht, Netherlands

***Correspondence:**
Anthony J. Porcelli, Department of Psychology, Marquette University, 604 North 16th Street CH317, Milwaukee, WI 53233, USA.
e-mail: anthony.porcelli@marquette.edu;
Mauricio R. Delgado, Department of Psychology, Rutgers University, 101 Warren Street, Newark, NJ 07102, USA.
e-mail: delgado@psychology.rutgers.edu

People often make decisions under aversive conditions such as acute stress. Yet, less is known about the process in which acute stress can influence decision-making. A growing body of research has established that reward-related information associated with the outcomes of decisions exerts a powerful influence over the choices people make and that an extensive network of brain regions, prominently featuring the striatum, is involved in the processing of this reward-related information. Thus, an important step in research on the nature of acute stress' influence over decision-making is to examine how it may modulate responses to rewards and punishments within reward processing neural circuitry. In the current experiment, we employed a simple reward processing paradigm – where participants received monetary rewards and punishments – known to evoke robust striatal responses. Immediately prior to performing each of two task runs, participants were exposed to acute stress (i.e., cold pressor) or a no stress control procedure in a between-subjects fashion. No stress group participants exhibited a pattern of activity within the dorsal striatum and orbitofrontal cortex (OFC) consistent with past research on outcome processing – specifically, differential responses for monetary rewards over punishments. In contrast, acute stress group participants' dorsal striatum and OFC demonstrated decreased sensitivity to monetary outcomes and a lack of differential activity. These findings provide insight into how neural circuits may process rewards and punishments associated with simple decisions under acutely stressful conditions.

Keywords: acute stress, cold pressor, reward processing, dorsal striatum, orbitofrontal cortex, fMRI, cortisol

INTRODUCTION

Human decision-making often occurs under stressful conditions. The type of stress exposure may be intrinsic or inherent to the decision itself (e.g., choosing between two desirable, but costly options with important consequences) or extrinsic, a pre-existing state which influences decision-making (e.g., stress exposure leading a person to use drugs as a coping mechanism). Thus, understanding how stress exposure influences decision-making is a topic of great interest. Recent efforts suggest that acute stress can modulate risk-taking in decision-making (Preston et al., 2007; Mather et al., 2009; Porcelli and Delgado, 2009), conditioning (for review, see Shors, 2004), and reinforcement learning critical to guiding future decisions (Cavanagh et al., 2010; Petzold et al., 2010). However, less is known about the impact of stress exposure on the processing of affective outcomes, a critical aspect of decision-making. The goal of the current experiment was to examine the influence of exposure to acute stress on reward-related responses in neural circuitry during the delivery of monetary rewards and punishments.

A rich animal literature has delineated a network of regions involved in processing reward-related information, also used to inform decision-making in the human brain (for review, see Schultz, 2006; Balleine et al., 2007; Haber and Knutson, 2010). This reward-related corticostriatal circuitry consists of prefrontal cortex (PFC) regions such as medial PFC and orbitofrontal cortex (OFC) as well as subcortical limbic regions involved in motivation and affect, including the dorsal and ventral striatum. The multifaceted striatum is of particular importance in coding for the subjective value of reward-related information critical to evaluation of outcomes associated with decisions (for review, see O'Doherty et al., 2004; Delgado, 2007; Rangel et al., 2008). Notably, components of the same reward-related neural circuitry have been implicated as a target of the physiological and neurochemical changes associated with engagement of the stress response.

Two complementary biological systems activated by acute stress exposure may influence brain regions involved in reward processing: the sympatho-adrenomedullary axis (i.e., the sympathetic branch of the autonomic nervous system or ANS) and the hypothalamic-pituitary-adrenal axis (HPA; for review, see Ulrich-Lai and Herman, 2009). In response to stress-related homeostatic disruption, the sympathetic ANS quickly responds with the release of catecholamines (CA; e.g., noradrenaline) from the adrenal medulla and ascending CA neurons in communication with the brainstem. As CA release in the peripheral nervous system promotes rapid excitatory changes within the body that enable an organism to deal with the source of the disruption (i.e., the classic "fight-or-flight" response; Cannon, 1915), signals of homeostatic disruption from the brainstem contribute to activation of the HPA via projections to the paraventricular nucleus of the hypothalamus. Proceeding at a slower pace, HPA activation ultimately results in the release of glucocorticoids from the adrenal cortex (i.e.,

cortisol in humans, corticosterone in rodents; Lupien et al., 2007).

Overall, the influence of acute stress has been studied in the context of memory and other cognitive processes (Joels et al., 2006), but less is known about the impact of stress on processing of reward-related information. One prominent idea is that stress may promote a shift from goal-oriented decision-making toward habit-based decisions that are insensitive to one's current environment, and can be maladaptive in some contexts (Schwabe and Wolf, 2011; Schwabe et al., 2012). This is supported by studies highlighting changes in structure and function of striatal regions involved in reward-related learning and habit-based decisions (e.g., Delgado, 2007; Tricomi et al., 2009; Balleine and O'Doherty, 2010). For example, rats exposed to chronic stress exhibit marked degradation of dorsomedial striatum and medial PFC with concurrent augmentation of the dorsolateral striatum associated with sustained habitual responses to stimuli even when altered decision outcomes devalue those responses (Dias-Ferreira et al., 2009). In humans, stress-related reductions in reward-related medial PFC responses have been observed in a task involving monetary rewards or neutral outcomes (Ossewaarde et al., 2011), while exposure to acute stress has been linked to reductions in dorsomedial striatal responses to a primary reward (i.e., food; Born et al., 2009).

The current literature suggests that acute stress may modulate neural systems involved in reward processing, particularly the striatum, but a direct test of this hypothesis in humans has not yet been made. The goal of the current study was to utilize a simple reward processing paradigm known to evoke robust striatal responses to examine the influence of exposure to acute stress on outcome evaluation. A potent secondary reinforcer was used: monetary rewards and punishments. A variant of a card guessing task was employed which involved asking participants to make a choice regarding a hidden number on a virtual "card" (Delgado et al., 2000). When participants guessed correctly, they received a monetary reward. When they guessed incorrectly, they received a monetary punishment. Furthermore, rewards and punishments varied in magnitude (high or low). In past research, performance on this task has been shown to evoke robust fMRI blood-oxygen-level-dependent (BOLD) responses in striatal regions. We hypothesized that the previously characterized differential response between rewards and punishments in the striatum would be reduced after exposure to acute stress.

MATERIALS AND METHODS

PARTICIPANTS

Thirty-four individuals participated in the study. Two participants were excluded from final data analysis, one due to an MRI equipment failure and the other resulting from a request to withdraw from participation. Thus, final data analysis was performed on 32 participants (16 females, 16 males; mean age = 23.41 years, SD years = 4.07). Participants responded to IRB-approved advertisements describing the study. The advertisements also indicated that compensation would be offered for their time at a rate of $25 per hour. All participants gave informed consent according to the guidelines of the Institutional Review Boards of the University of Medicine and Dentistry of New Jersey and Rutgers University.

PROCEDURE

Stress induction

Participants were exposed to acute stress in a between-subjects fashion using a variant on the traditional cold pressor task, which involves immersion of one's hand into a container of ice-cold water. It is important to note that although water is not inherently incompatible with the MRI environment, if spilled it can be a threat to sensitive MRI equipment (such as the head coil). Additionally, even in the absence of damage due to a spill water can interfere with MRI signal due to its high proton density (Huettel et al., 2008). In the current experiment, we adapted the cold pressor test to fit the MRI environment. To administer cold pressor stress safely once participants were placed within the MRI, rather than prior to entry, an arm wrap was created from a combination of MRI-compatible dry gelpacs and maintained at a temperature of approximately 4°C. This "cold pressor arm wrap" was placed around the right hand and arm of participants assigned to the acute stress group for 2 min immediately prior to each of the two card guessing tasks. For participants assigned to the no stress group, a similar wrap created from towels (at room-temperature) was applied to control for tactile stimulation of the cold pressor arm wrap prior to each card guessing task. Hereafter, when making reference to the two groups collectively the term "experimental groups" will be used.

Card guessing task

In the card guessing task (adapted from Delgado et al., 2000; Delgado et al., 2003) participants were presented with a virtual "card" upon which a question mark was printed for 2 s, representing a number between 1 and 9 (**Figure 1A**). Their task was to make a button press during those 2 s indicating whether they believed the number on the card was higher or lower than the number 5 (choice phase). After making their response during the 2 s choice phase, the actual number appeared on the card for 2 s (outcome phase). If participants had made a correct guess, they received a monetary reward. If their guess was incorrect, they received a monetary punishment. Rewards and punishments could be of high or low magnitude (reward: +$5.00 or +$0.50; punishment: −$2.50 or −$0.25). Importantly, values were manipulated to account for increased sensitivity to monetary losses over gains (i.e., loss aversion), thus ensuring that variations in BOLD signal related to rewards were comparable to those associated with punishments (Tversky and Kahneman, 2004). The magnitude of a reward was concurrently presented during the 2 s outcome phase via presentation of five green check marks (high magnitude) or one green check mark (low magnitude) below the card's indicated number. Similarly, the magnitude of monetary punishments was represented by five red "×" marks (high magnitude) or one red "×" mark (low magnitude). Participants were explicitly informed as to the monetary value associated with each stimulus prior to beginning the task, but actual dollar amounts were not presented during the task (only the check and × marks). A jittered inter-trial-interval followed the outcome phase during which participants viewed a fixation lasting between 10 and 12 s, followed by the next trial.

Participants engaged in two runs of the card guessing task and were informed that they would receive compensation consistent with their performance (i.e., the outcomes they were presented

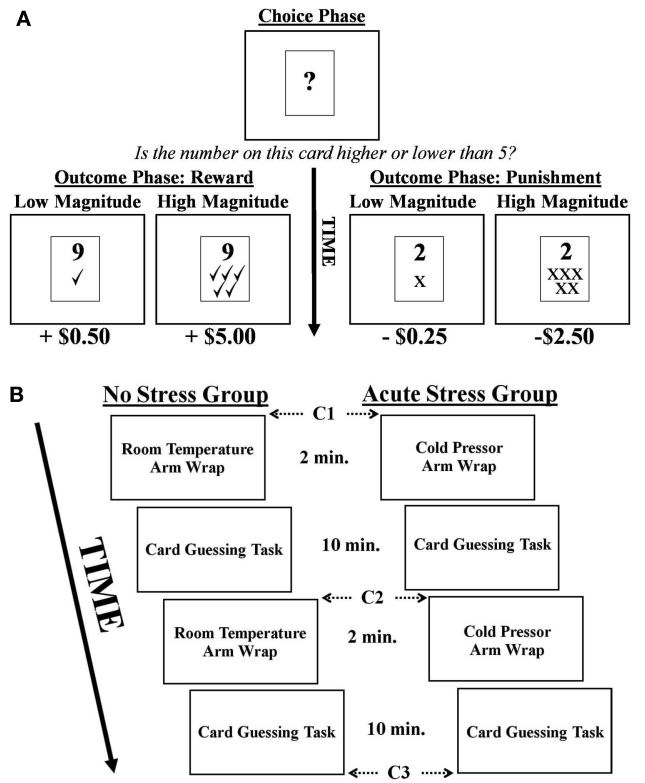

FIGURE 1 | (A) Depiction of the card guessing task. Note, in the example above a correct choice would be "higher than five." **(B)** Experimental timeline and cortisol sampling schedule (C = cortisol sample).

with) during the card guessing task. Each run involved 40 trials with a total run time of 10 min. Participants were unaware that the outcome of each trial was predetermined such that a balanced presentation of rewards and punishments, as well as high and low magnitudes, was maintained. Thus, of the 40 trials per run 20 were associated with rewards and 20 with punishments, 10 of high/low magnitude for each valence. After completion of the experiment, participants were debriefed as to the actual nature of the task. They then completed a post-experimental questionnaire where they rated subjective stress levels associated with the arm wrap on a seven point Likert scale, as well as how the wrap made them feel (good or bad).

Salivary cortisol measurements

Participants were instructed to avoid eating, drinking (anything other than water), or smoking for 2 h prior to the beginning of the experiment to ensure that saliva samples were untainted. To acquire salivary cortisol data, participants were asked to moisten a Salimetrics Oral Swab (SOS) in their mouths for about 1 min by placing the SOS underneath their tongue. Upon completion of this procedure, the subject withdrew the SOS and the experimenter immediately placed it in an individual centrifuge tube. Three samples were acquired for each participant interspersed throughout the scanning session in approximately 15 min intervals, with the first sample taken after anatomical MRI scans were completed (prior to the first card guessing task). Samples two and three were acquired after each of the two blocks of the card guessing task. Samples were frozen in cold storage at −10°C, packed with dry ice and sent to Salimetrics Laboratory (State College, PA, USA) for duplicate biochemical assay analysis. An experimental timeline and cortisol sampling schedule is presented in **Figure 1B**. Importantly, female participants were screened for use of oral contraceptives (OC) that might influence cortisol levels (though this information was not used as an exclusionary criterion *per se*). Although 5 of the 16 female participants did report use of OC, no significant differences in cortisol levels were observed between OC and non-OC participants as measured by repeated-measures ANOVA. Furthermore, when those five participants were excluded from the imaging analysis the significance and directionality of all reported effects remained unchanged.

fMRI ACQUISITION AND ANALYSIS

Imaging was performed on a 3T Siemens Allegra scanner equipped with a fast gradient system for echoplanar imaging. A standard radiofrequency head coil with foam padding was used to restrict participants' head motion while minimizing discomfort. High-resolution axial images (T1-weighted MPRAGE: 256 × 256 matrix, FOV = 256 mm, 176 1 mm axial slices) were obtained from all subjects. Functional images (single-shot gradient echo EPI sequence; TR = 2000 ms; TE = 25 ms; FOV = 192 cm; flip angle = 80°; matrix = 64 × 64; slice thickness = 3 mm) were acquired during performance on the two card guessing task runs. Data were then preprocessed and analyzed using BrainVoyager QX software (version 2.2, Brain Innovation, Maastricht, Netherlands). Preprocessing involved motion correction (six-parameter, three-dimensional), spatial smoothing (4-mm FWHM), voxelwise linear detrending, high-pass filtering of frequencies (three cycles per time course) and normalization to Talairach stereotaxic space (Talairach and Tournoux, 1988).

General linear models (GLM) were defined at the single-subject level in which predictors were regressed onto the dependent variable of BOLD changes within the brain. Two separate models were generated. In model 1 (outcome valence only), two predictors modeled the outcome phase of the card guessing task based on whether participants had received a rewarding outcome (gain of money) or punishing outcome (loss of money) after their choice. For model 2 (outcome valence and outcome magnitude), the magnitude of rewards and punishments were included, resulting in a model comprised of four predictors: high magnitude reward, low magnitude reward, high magnitude punishment, and low magnitude punishment. In both models, motion parameters generated during fMRI data preprocessing were included as covariates of no-interest (to control for head motion), as was a missed-trial predictor. Two second-level random effects GLMs were then performed.

Based on the random effects GLMs whole-brain statistical parametric maps were generated. Given *a priori* patterns of BOLD signal defined by a similar contrasts in past work (for review, see Delgado, 2007) it was thought that a Reward – Punishment contrast would best highlight task-related alterations in BOLD signal in regions of the brain known to be involved in processing reward-related information. Using model 1 (outcome

valence only) a whole-brain two-tailed contrast was performed on outcome phase BOLD in which rewards and punishments were received (Reward – Punishment), and the difference in BOLD associated with this contrast was contrasted along the between-subjects factor of experimental group (No Stress vs. Acute Stress). Thus, this analysis highlighted brain regions responsive to outcome valence that significantly differed between experimental groups. In a similar whole-brain analysis using model 2, a contrast of high and low magnitude outcomes across outcome valence was performed ([High Reward + High Punishment] – [Low Reward + Low Punishment]) and the difference in BOLD associated with this contrast was computed along the between-subjects factor of experimental group (No Stress vs. Acute Stress). Therefore, this analysis examined brain regions responsive to the magnitude of monetary outcomes that significantly differed between experimental groups.

The resultant contrast maps were then examined to identify statistically significant clusters of activation at a threshold of $p < 0.005$, with a contiguity threshold of 5^3 mm voxels. Correction for multiple comparisons was verified through the use of cluster-size thresholding (Forman et al., 1995; Goebel et al., 2006). Thus, only clusters of a sufficient extent so as to be associated with a cluster-level false-positive rate of $\alpha = 0.05$ remained in the analysis. Additionally, an exploratory analysis of the possible role of participants' sex was performed in *a priori* regions of interest given previous sex-related effects observed in the literature (e.g., Lighthall et al., 2011). Specifically, parameter estimates were extracted from significant clusters resultant from both contrasts and examined for potential interactions with sex. Importantly, all *post hoc* tests within each family of analyses were corrected for multiple comparisons via sequential Bonferroni correction (Holm, 1979).

RESULTS

REACTION TIME DATA

A two-tailed independent *t*-test was performed to examine differences in reaction time in the card guessing task between experimental groups. No significant difference was observed in reaction times for the acute stress ($M = 623.31$, SEM = 45.91) vs. no stress ($M = 633.77$, SEM = 43.81) groups, $t(30) = 0.17$, $p > 0.15$, $d = 0.06$.

SUBJECTIVE STRESS RATINGS

Post-experimental subjective ratings of perceived stress experience were examined between acute stress and no stress experimental groups via independent *t*-tests. These included ratings of how the cold pressor arm wrap made participants feel (good to bad) and how stressful (high to low) the experience was. Compared to the no stress group, the acute stress group rated the arm wrap as feeling significantly worse [$t(30) = 4.42$, $p < 0.001$, $d = 1.56$] and more stressful [$t(30) = 3.46$, $p < 0.01$ $d = 1.22$].

SALIVARY CORTISOL DATA

Salivary cortisol data were excluded for three participants, in one case due to a corruption of the samples and in two cases due to an inability to acquire samples during MRI scanning. Thus, cortisol analyses were conducted on 29 of the 33 participants (13 no stress, 16 acute stress). Mean salivary cortisol levels (in nmol/L) for all three samples by experimental group are reported in **Table 1**. A 3 (Sample 1, 2, or 3) × 2 (Experimental Group: No Stress vs. Stress) repeated-measures ANOVA was performed, but no significant interaction between sample and experimental group was observed, $F(2, 54) = 1.77$, $p = 0.18$, $\eta_p^2 = 0.061$. Area under the curve with respect to increase (AUC_I) was calculated using the trapezoidal method for both experimental groups. This measure is useful in that it represents both time-related changes in salivary cortisol levels as well as the overall intensity of said changes (Pruessner et al., 2003). A one-tailed independent *t*-test between AUC_I for the experimental groups (No stress vs. Acute Stress) indicated a significant increase in cortisol levels for those participants who were exposed to acute stress, $t(27) = 1.78$, $p < 0.05$, $d = 0.69$ (**Figure 2**). No significant correlations were observed between cortisol and imaging data presented below.

fMRI RESULTS

Outcome valence: reward – punishment by experimental group contrast

In the no stress group, multiple brain regions demonstrated greater BOLD signal associated with the reward – punishment contrast than were observed in the acute stress group (see **Table 2**). Prominently featuring among these regions were the dorsal striatum (specifically the right caudate nucleus and left putamen) and the left OFC.

In the right caudate, *post hoc* paired *t*-tests suggested that BOLD signal in the no stress group was significantly greater for rewards than punishments, $t(15) = 5.69$, $p < 0.001$, $d = 0.88$

Table 1 | Mean salivary cortisol levels in nmol/L at baseline, after task run 1, and after task run 2 by experimental group (Mean ± SEM).

Sample (nmol/L)	Experimental group	
	No stress	Acute stress
Baseline (min)	3.93 ± 0.52	3.80 ± 0.28
Post-baseline 1 (∼15)	3.61 ± 0.45	4.23 ± 0.54
Post-baseline 2 (∼30)	3.31 ± 0.38	3.67 ± 0.42

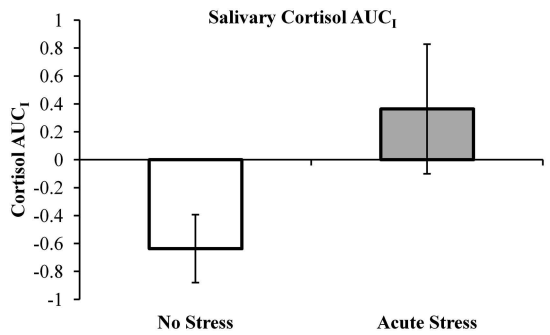

FIGURE 2 | Salivary cortisol area under the curve with respect to increase (AUC_I) by experimental group. Note, negative AUC_I values (indicating a decrease in salivary cortisol over the course of the experiment) were retained as an "index of decrease" as recommended by Pruessner et al. (2003).

Table 2 | Brain regions that demonstrated differences by experimental group (No Stress vs. Acute Stress) for Reward – Punishment and High – Low Magnitude contrasts ($p < 0.005$, corrected).

Activated region	Laterality	Talairach coordinates			Voxel count (mm^3)	*T*-value
		x	*y*	*z*		
REWARD – PUNISHMENT (NO STRESS > ACUTE STRESS GROUP)						
Superior parietal lobule (BA 7)	R	38	−65	48	355	4.24
Middle frontal gyrus (BA 6)	R	41	13	45	239	4.74
Inferior parietal lobule (BA 40)	R	41	−38	42	2693	5.58
Middle frontal gyrus (BA 9)	R	35	31	30	1382	5.48
Middle frontal gyrus (BA 9)	L	−28	13	30	135	4.70
Precentral Gyrus (BA 6)	R	35	4	27	152	5.25
Caudate (dorsal striatum)	R	14	4	18	206	3.74
Putamen (dorsal striatum)	L	−22	4	6	138	4.43
Orbitofrontal cortex (BA 47)	L	−40	43	−6	170	3.81
Middle temporal gyrus (BA 21)	R	53	−32	−9	188	4.35
Inferior temporal gyrus (BA 37)	R	53	−53	−12	137	4.13
Inferior temporal gyrus (BA 20)	L	−55	−26	−18	146	4.31
Fusiform gyrus (BA 20)	L	−58	−14	−24	186	4.22
REWARD – PUNISHMENT (ACUTE STRESS > NO STRESS GROUP)						
Cuneus/posterior cingulate (BA 18/31)	L	−25	−56	6	177	−4.22
HIGH – LOW MAGNITUDE (NO STRESS > ACUTE STRESS GROUP)						
Inferior frontal gyrus (BA 45)	L	−58	13	18	873	5.77

BA, Brodmann Area; L, left; R, right.

(**Figures 3A–C**). No significant difference was observed in the acute stress group, $t(15) = 0.74$, $p > 0.15$, $d = 0.08$. A similar pattern of BOLD signal was observed in the left putamen [no stress, $t(15) = 6.57$, $p < 0.001$, $d = 0.73$; acute stress, $t(15) = 1.24$, $p > 0.15$, $d = 0.18$] and left OFC [no stress, $t(15) = 6.80$, $p < 0.001$, $d = 1.15$; acute stress, $t(15) = 0.37$, $p > 0.15$, $d = 0.06$; see **Figure 4**]. Thus, whereas the no stress group demonstrated a clear response to rewards over punishments in these regions, the group that had been exposed to acute stress exhibited a lack of responsiveness to reward-related information. All significant *t*-tests survived sequential Bonferroni correction.

Parameter estimates for these three regions in the acute stress group were then examined in a second analysis for the presence of magnitude-related effects (an orthogonal factor not included in the original contrast) in reward and punishment trials. In the right caudate, *post hoc* paired *t*-tests suggested that BOLD signal in the acute stress group was significantly greater for rewards over punishments for outcomes of high magnitude, $t(15) = 2.79$, $p < 0.05$, $d = 0.31$, but not low magnitude, $t(15) = -1.37$, $p > 0.15$, $d = -0.25$. A similar pattern was observed within the left putamen. Acute stress group BOLD differentiated between high magnitude outcomes, $t(15) = 2.84$, $p < 0.05$, $d = 0.43$, but not low magnitude outcomes, $t(15) = -0.83$, $p > 0.15$, $d = -0.20$. Notably, in contrast to the above regions the left OFC in the acute stress group did not significantly differentiate between outcomes of either magnitude [high: $t(15) = 1.25$, $p > 0.15$, $d = 0.27$; low: $t(15) = -1.71$, $p > 0.10$, $d = -0.34$]. All significant *t*-tests survived sequential Bonferroni correction.

To examine whether or not a difference was present in the stress effect between the two task runs, a region of interest (ROI) analysis was performed investigating right dorsal striatum, left putamen, and left OFC BOLD signal between runs 1 and 2 (using ROIs from the original whole-brain analysis). Parameter estimates extracted from the three aforementioned ROIs were examined via 2 (Run: Run 1 vs. Run 2) × 2 (Outcome Valence: Reward vs. Punishment) × 2 (Experimental Group: No Stress vs. Acute Stress) repeated-measures ANOVA for the purpose of establishing whether or not a difference in BOLD existed as a function of run. No significant interaction was observed between run, experimental group, and outcome valence in the right dorsal striatum, $F(1, 30) = 0.001$, $p > 0.15$, $\eta_p^2 = 0.000$, left putamen, $F(1, 30) = 0.77$, $p > 0.15$, $\eta_p^2 = 0.025$, or left OFC, $F(1, 30) = 0.31$, $p > 0.15$, $\eta_p^2 = 0.010$, suggesting that the previously discussed effects were not different between runs.

Outcome magnitude: high – low by experimental group contrasts

A single brain region was associated with increased BOLD signal for no stress participants in the outcome magnitude contrast: the left inferior frontal gyrus (BA45). *Post hoc* paired *t*-tests indicated that no stress participants showed greater BOLD responses to high over low magnitude outcomes (across outcome valence), $t(15) = 4.77$, $p < 0.001$, $d = 0.76$. Acute stress participants, however, demonstrated a trend (which did not survive Bonferroni–Holm correction) toward the reverse pattern – increased BOLD for low over high magnitude outcomes, $t(15) = -1.98$, $p < 0.10$, $d = -0.38$.

Exploratory analyses: sex effects

Salivary cortisol AUC_I was examined via univariate ANOVA for sex-related differences in cortisol increases by experimental

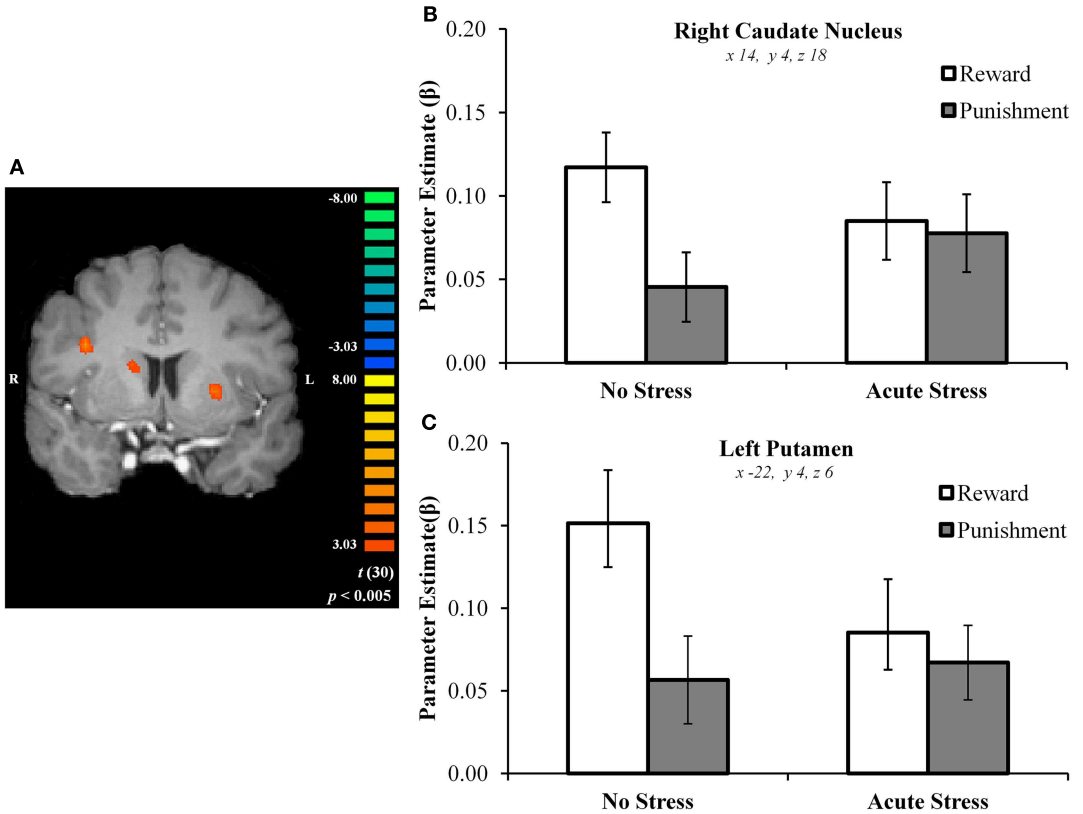

FIGURE 3 | (A) Right caudate and left putamen clusters exhibiting greater BOLD signal for no stress over acute stress participants. **(B)** Right caudate nucleus outcome valence × experimental group parameter estimates. **(C)** Left putamen outcome valence × experimental group parameter estimates.

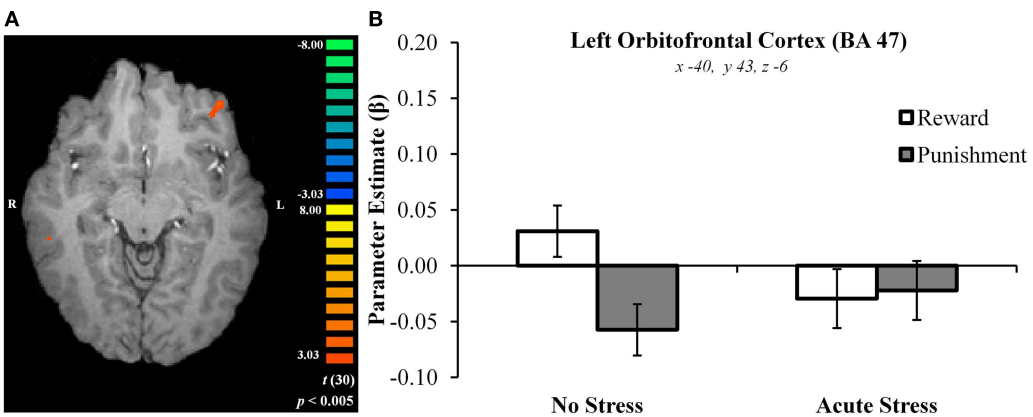

FIGURE 4 | (A) Left orbitofrontal cortex cluster exhibiting greater BOLD signal for no stress over acute stress participants. **(B)** Left orbitofrontal cortex outcome valence × experimental group parameter estimates.

group. No significant main effect of sex on salivary cortisol was observed, $F(1, 25) = 0.52$, $p = 0.48$, $\eta_p^2 = 0.020$, nor was a significant sex by experimental group interaction observed, $F(1, 25) = 0.03$, $p = 0.87$, $\eta_p^2 = 0.001$. Parameter estimates extracted from significant clusters in both contrasts were subjected to a series of 2 (Outcome valence: Reward vs. Punishment) × 2 (Experimental Group: No Stress vs. Acute Stress) × 2 (Sex: male vs. female) repeated-measures ANOVAs to explore -the possible role of sex in stress-related differences in processing of reward-related information. In the right caudate a trend towards a significant experimental group × sex interaction was observed, $F(1, 28) = 3.27$, $p < 0.10$, $\eta_p^2 = 0.105$. *Post hoc* independent

t-tests indicate that no stress group female participants exhibited greater BOLD signal overall for all outcomes than did males, $t(14) = -2.57$, $p < 0.05$, $d = -1.28$. In contrast acute stress group males' BOLD was elevated as compared to the no stress group whereas females' was reduced, resulting in a non-significant difference between the sexes, $t(14) = 0.44$, $p > 0.15$, $d = 0.22$. No other brain regions exhibited trending or significant sex effects.

DISCUSSION

In this study, we sought to investigate how exposure to acute stress influenced neural responses to monetary rewards and punishments. We used a between-subjects approach and tested performance of participants after application of a cold pressor procedure (acute stress group), compared to a control procedure (no stress group) during two runs of a simple card guessing paradigm previously found to yield robust striatal activation to reward responses (e.g., Delgado et al., 2000). Salivary cortisol data and subjective stress ratings confirmed that the stressor (i.e., cold pressor arm wrap adapted for fMRI) was effective. Participants exposed to acute stress exhibited a marked alteration in neural responses to monetary rewards and punishments. Whereas dorsal striatal BOLD signal within the right caudate nucleus and left putamen differentiated between rewarding and punishing outcomes in no stress participants, this was not the case in acute stress participants. A similar pattern of activity was observed in the left OFC. Notably, high magnitude rewards and punishments were resilient to the stress effect in striatal regions but not within OFC. Taken together, these results suggest that exposure to acute stress affects reward-related processing in the dorsal striatum and OFC.

This study complements and augments a growing literature examining the influence of acute stress on human decision-making by attempting to characterize striatal responses to outcome processing under stress. Previous studies have shown modulation of striatal response under stress using different paradigms and reinforcers. For instance, acute stress-related reductions in putamen responses to primary rewards (food images) have been observed (Born et al., 2009), which complements the outcome processing of secondary reinforcers in the current paradigm observed in both caudate and putamen. The consequences of decreased sensitivity to reward processing is a question for future research, but it is informed by a recent study suggesting that increased life stress and reduced ventral striatum reactivity to rewards (i.e., positive performance feedback) interact to predict low levels of positive affect on a depression scale (Nikolova et al., 2012). This converges with previous behavioral work indicating a reduction in responsiveness to rewards under acute stress (Bogdan and Pizzagalli, 2006) which the current study builds upon with the observation of reductions in reward-related responses in the dorsal striatum after acute stress exposure.

An interesting observation from our study is that the stress modulation effect was observed in the dorsal, but not the ventral, striatum. A null finding, however, should not be interpreted as a lack of stress modulation of ventral striatum responses (in fact, stress-related ventral striatal activation has been observed in a non-reward-related task; Pruessner et al., 2008); rather, it highlights the sensitivity of dorsal striatum activity to stress modulation (e.g., Sinha et al., 2005). The dorsal striatum, particularly the caudate, has often been found to be robustly recruited by the reward paradigm used in the current paper (for review, see Delgado, 2007). Further, the dorsal striatum has been posited to function as an "actor" that maintains information about action-contingent response-reward associations to guide future decisions based on the outcomes of past ones, while the ventral portion a "critic" that predicts possible future rewards (O'Doherty et al., 2004; Tricomi et al., 2004). Thus, by impairing the ability of the dorsal striatum to distinguish between rewarding vs. punishing outcomes, acute stress may interfere with the use of information provided by past decisions to guide future choices.

Within the dorsal striatum itself, a functional subdivision suggests that the medial portion of the dorsal striatum is involved in flexible, goal-oriented, and action-contingent decision-making whereas the lateral portion mediates habitual and stimulus bound decisions (Balleine et al., 2007; Tricomi et al., 2009). In the current experiment, it is plausible that stress-related changes in BOLD signal observed in the dorsomedial striatum (i.e., caudate) and dorsolateral striatum (i.e., putamen) mark the beginning of a shift from goal-directed to habitual processing of decision outcomes, although further work is necessary to test this hypothesis using an affective learning paradigm. The hypothesis is consistent with previous behavioral work in support of stress' ability to shift decision-related processing from goal-oriented to habitual (i.e., as in instrumental conditioning; Schwabe and Wolf, 2011). Importantly, decreased sensitivity to reward processing in the dorsal striatum may have important clinical applications with respect to decision-making and one's general affect. For instance, stress- and drug-cue associated alterations in dorsal striatal function have been implicated in relapse in drug/alcohol addiction (Sinha and Li, 2007) and reduced dorsal striatal responses to rewards have been observed in unmedicated individuals suffering from major depressive disorder (Pizzagalli et al., 2009).

Another brain region implicated in processing of reward-related information is the OFC, which in this experiment also exhibited alterations in responsiveness to rewards and punishments. It has been suggested that this region may be involved in outcome evaluation by coding for the subjective value of said decision outcomes (O'Doherty et al., 2001a). For example, increases in OFC BOLD have been observed during delivery of pleasant as compared to aversive gustatory stimuli (O'Doherty et al., 2001b). Although stress-related reductions in brain function during reward processing have been somewhat studied in neighboring prefrontal regions such as the medial PFC (Ossewaarde et al., 2011) OFC has received less attention in this regard, making it an ideal topic for future research. This is especially the case with respect to the effects of stress on drug addiction, as this region may play a role in the inability of addicts to alter their behavior based on likely outcomes or consequences – leading to relapse (Schoenbaum and Shaham, 2008). A notable exception is a recent study suggesting the necessity of concurrent CA and glucocorticoid activation in reductions in OFC sensitivity to reward-related information (e.g., Schwabe et al., 2012).

With respect to the mechanism underlying the findings of the current study, several plausible interpretations can be considered. It has been established that glucocorticoid responses to

cold pressor stress are less extreme than have been observed in other stress induction techniques, such as stressors involving a psychosocial component (e.g., McRae et al., 2006; Schwabe et al., 2008). In the current study, this is reflected by mild-to-moderate acute stress group increases in cortisol. In contrast, it is likely that sympathetic ANS activation remains comparable between cold pressor and other forms of stress. Another consideration is that in the current study initial acute stress exposure occurred immediately prior to the first card guessing task, followed 15 min later by a second stress exposure and card guessing task. As the effects of glucocorticoid release in this type of paradigm would likely be genomic (i.e., slow and long-lasting; Sapolsky et al., 2000) it is possible that they did not influence brain function in the first task run. Yet, the observed decrease in striatal and OFC responsiveness to reward-related information was present in both task runs. Further, as stress-related increases in cortisol were modest here it is possible that glucocorticoids did not contribute to the effect at all. Thus, lack of data that can speak to the dynamics of sympathetic ANS activation (e.g., skin conductance or salivary alpha amylase; Rohleder et al., 2004) constitutes a study limitation. While the paradigm employed here was not designed to address these issues, it is likely that contextual factors including the nature and timing of stress exposure and the mode of reward-related information involved in the task play an important role.

Some studies suggest that sex differences may play a role in stress-related alterations in striatal reward processing. For example, studies examining the influence of acute stress on risk-tasking have established fluctuations in dorsal striatal function as a function of gender (Lighthall et al., 2009, 2011). There participants performed the Balloon Analog Risk Task, which involves making a button press to expand a virtual balloon for monetary rewards. With each button press, more money is gained – but at a certain point the balloon will explode. Thus, participants risk losing all winnings if they continue to expand the balloon to gain additional rewards. It was observed that under acute stress males take more risks and exhibit increases in dorsal striatal function, whereas females show the reverse pattern, as compared to no stress participants. In the current study, a trend toward a sex difference along similar lines was also observed in the dorsal striatum – though to a lesser degree. No stress females' BOLD for outcomes was elevated above males'. While BOLD signals to outcomes did decrease for acutely stressed females and increased for males, the result was more extreme in the Lighthall et al. (2009, 2011) studies. This may relate to the fact that risk-taking tasks such as the balloon task involve anticipation of potential outcomes in addition to an outcome evaluation component, while also requiring participants make complex choices balancing potential rewards against potential punishments. It may be the case that the simple outcome evaluation paradigm used in our study is less sensitive to sex differences than more dynamic and complex risk-taking paradigms.

In sum, this paper used a novel approach to induce stress in the fMRI scanner (the cold pressor arm wrap) and observed that exposure to acute stress modulated reward-related circuitry. Specifically, participants under stress showed decreased differential responses to reward and punishment in the dorsal striatum and OFC. Future studies may try to probe if this decreased differential response is driven by a diminished response to rewards (as previously observed in the literature, e.g., Born et al., 2009) or an increase in sensitivity to negative outcomes. Further, additional research is needed to clarify how neural responses to these distinct reinforcers might influence subsequent decision-making under stress.

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Decision making in the reward and punishment variants of the Iowa gambling task: evidence of "foresight" or "framing"?

Varsha Singh[1,2]* and Azizuddin Khan[3]

[1] *Department of Organizational Behavior and Human Resources, Indian Institute of Management, Kozhikode, India*
[2] *Department of Management, Indian Institute of Science, Bangalore, India*
[3] *Department of Psycho-physiology laboratory, Humanities and Social Sciences, Indian Institute of Technology, Mumbai, India*

Edited by:
Ben Seymour, University of Osaka, Japan

Reviewed by:
Bruno B. Averbeck, National Institute of Mental Health, USA
Mauricio R. Delgado, Rutgers-Newark: The State University of New Jersey, USA

****Correspondence:***
Varsha Singh, Department of Management, Indian Institute of Science, Bangalore 560012, India.
e-mail: vsingh.iitb@gmail.com

Surface-level differences in the reward and punishment variants, specifically greater long-term decision making in the punishment variant of the Iowa Gambling Task (IGT) observed in previous studies led to the present comparison of long-term decision making in the two IGT variants ($n = 320$, male = 160). It was contended that risk aversion triggered by a positive frame of the reward variant and risk seeking triggered by a negative frame of the punishment variant appears as long-term decision making in the two IGT variants. Apart from the frame of the variant as a within-subjects factor (variant type: reward and punishment), the order in which the frame was triggered (order type: reward–punishment or punishment–reward), and the four types of instructions that delineated motivation toward reward from that of punishment (reward, punishment, reward and punishment, and no-hint) were hypothesized to have an effect on foresighted decision making in the IGT. As expected, long-term decision making differed across the two IGT variants suggesting that the frame of the variant has an effect on long-term decision making in the IGT ($p < 0.001$). The order in which a variant was presented, and the type of the instructions that were used both had an effect on long-term decision making in the two IGT variants ($p < 0.05$). A *post hoc* test suggested that the instructions that differentiated between reward and punishment resulted in greater foresight than the commonly used IGT instructions that fail to distinguish between reward and punishment. As observed in previous studies, there were more number of participants (60%) who showed greater foresight in the punishment variant than in the reward variant ($p < 0.001$). The results suggest that foresight in IGT decision making is sensitive to reward and punishment frame in an asymmetric manner, an observation that is aligned with the behavioral decision making framework. Benefits of integrating findings from behavioral studies in decision neuroscience are discussed, and a need to investigate cultural differences in the IGT studies is pointed out.

Keywords: Iowa gambling task, reward–punishment, instructions, decision making, framing effect

INTRODUCTION

The somatic marker hypothesis (SMH) states that emotions are indispensible to long-term decision making (Damasio, 1994). Support for the hypothesis comes from observing healthy participants' ability to make long-term advantageous decisions on a task called the Iowa gambling task (IGT; Bechara et al., 1994). In order to rule out reward and punishment sensitivity as an alternative explanation for decision making on the task, Bechara et al. (2000b) compared reward and punishment variants of the IGT to demonstrate long-term advantageous decision making irrespective of the immediate reward and punishment frame of the IGT. However, in the most examined reward variant, the magnitude (Tomb et al., 2002; van den Bos et al., 2006) and frequency of immediate reward and punishment (Chiu and Lin, 2007; Lin et al., 2007; Chiu et al., 2008) continue to confound long-term decision making in the IGT.

In the current paper, the effect of reward and punishment sensitivity on long-term decision making in the two variants is examined. Three observations have led to the current examination of the two variants. (1) In the original and subsequent studies, there are on-the-surface differences in long-term decision making in the two variants, such that higher long-term advantageous decision making is seen in the punishment variant (e.g., Bechara et al., 2000b, 2002; Must et al., 2006, 2007; Verdejo-Garcia et al., 2006). (2) Differences in long-term decision making in the two variants might be masked by using an unequal criterion for judging impairment in the two variants (i.e., a score less than 10 in the reward variant and less than 8 in the punishment variant; Bechara et al., 2002). Unequal cut-off criteria suggest a difference in the ability to make long-term advantageous decisions in the two variants. (3) Judging by the direction of inequality in the cut-off scores, long-term decision making in the punishment variant seems more difficult. However, more number of healthy participants were "impaired" in the reward variant and "unimpaired" in the punishment variant (56%), whereas only a small number

of participants (4.5%) showed the opposite trend (Bechara et al., 2002), suggesting greater difficulty in making long-term decision making in the reward variant.

A difference in long-term decision making in the two variants is expected based on the following extrapolation:

(1) Even though both the variants contain rewards and punishments the reward variant triggers a positive frame and the punishment variant triggers a negative frame. A brief description of the two variants will be helpful in understanding how the immediate "frame" of the variant might affect long-term decision making on the IGT. The reward variant offers a choice between four decks of cards labeled A′, B′, C′, and D′. The participant has to pick one card at a time; after a card is picked, an announcement of the amount "won" is flashed on the computer screen, occasionally followed by an announcement of a "loss." The punishment variant offers a choice between four decks of cards labeled E′, F′, G′, and H′. After a card is picked, the "loss" is announced, which at times is followed by a "gain." Therefore in spite of both the variants offering both, rewards and punishments, the prominent outcome in the reward variant is a "win," and in the punishment variant a "loss," which underlies the assertion that a positive frame (i.e., "gain") is triggered in the reward variant and a negative frame (i.e., "loss") is triggered in the punishment variant. Unknown to the decision maker, decks A′ and B′ have high immediate rewards and a net loss, while decks C′ and D′ have small immediate rewards and a net gain. Long-term advantageous decision making is reflected in avoiding the risky decks (decks A′ and B′) and seeking the safe decks (decks C′ and D′). In the punishment variant, decks F′ and H′ give immediate low losses and a low net gain, while decks E′ and G′ give immediate high losses and a high net gain. Long-term advantageous decision making is reflected in choosing high immediate punishment decks (decks E′ and G′) and avoiding low-immediate-punishment decks.

(2) The dominant behavioral response required for long-term decision making in the positive frame of the reward variant is avoidance of the risky decks (decks A′ and B′), and in the negative frame of the punishment variant, seeking of the risky decks or endurance of high immediate punishments (decks E′ and G′). It is possible that in the previous studies, risk aversion triggered in the reward variant resulted in safe choices (i.e., choice of decks C′ and D′) and risk taking triggered in the punishment variant resulted in choice of risky high immediate punishment (i.e., choice of decks E′ and G′), choice in both the variants appearing as long-term advantageous decision making. Therefore it is contended that long-term decision making in the two variants might demonstrate a "framing" effect (Tversky and Kahneman, 1981) rather than "foresight" and its immunity to reward–punishment sensitivity (Bechara et al., 1994).

The first step in testing the effects of reward and punishment frame in the IGT decision making taken was to test the effect of the variant type (i.e., reward and punishment frames of the IGT), and address a methodological problem that was observed in the previous studies, i.e., lack of a counter-balanced presentation of the variants (e.g., Bechara et al., 2000b, 2002; Verdejo-Garcia et al., 2006). The effect of the order in which the variant is presented would further indicate a "framing" effect suggesting that the order in which a frame is triggered also has an impact on foresighted decision making in the IGT.

To attribute the effect of variant type and order type to reward and punishment sensitivity, task motivation toward reward and punishment was altered via task instructions. Commonly used instructions for both the variants (henceforth standard instructions) are bi-directional (i.e., the decision maker is asked to seek rewards as well as avoid punishments; Bechara et al., 1994) and trigger sensitivity to both reward (gain), and punishment (loss). The standard instructions assume that long-term decision making is indifferent to reward and punishment (i.e., the decision maker is equally motivated to seek rewards and to avoid punishments). However, the standard instructions are known to convey risk-avoiding clues on which long-term decision making in the reward variant was dependent (Blair and Cipolotti, 2000; Balodis et al., 2006; Fernie and Tunney, 2006). It is possible that the only part of the standard instructions that directs one to avoid punishment is attended in the reward variant which would be compatible with the framing effect explanation. The uni-directional instructions (i.e., the decision maker is motivated either to seek rewards or to avoid punishments) will delineate sensitivity to rewards from that of punishment, and the effect of instruction alteration on long-term decision making in the two variants will indicate a pronounced framing effect or the effect of reward and punishment. In line with the assertion that reward and punishment sensitivity has an effect on IGT decision making, it was hypothesized that variant, order, and instruction types will have an effect on long-term decision making in the IGT.

MATERIALS AND METHODS

SAMPLE

Three-hundred twenty healthy undergraduate and graduate students volunteered for the study (mean age = 23.82; SD = 3.25 years; male = 160). All the participants had more than 18 years of education (22.7% were enrolled in a bachelor's program, 44.9% were enrolled in a master's program, and 32.4% were enrolled in a doctoral program). Most of the participants were right handed (86.1%) and non-smokers (93.6%). All the participants were medication-free, had never experienced a head injury that required hospitalization, and had never been diagnosed with a psychiatric illness.

DESIGN

A 2 (variant order: reward–punishment and punishment–reward) × 2 (variant type: total net score on reward and total net score on punishment variant) × 4 (instruction type: avoid punishment, seek reward, standard, and no-hint) design was used in the study. Within-subject variables were total net scores on the reward variant and the punishment variant, and between subject variables were type of order and type of task instruction used.

Decision making in the variants was analyzed according to the "net score" method (Bechara et al., 1994), that is, the number of

cards drawn from decks A′ and B′ are added and their sum is deducted from the number of cards drawn from decks C′ and D′ [(decks C′ + D′) − (decks A′ + B′)]. This is done for a block of 20 trials each, and scores on 5 blocks are added to get a total net score in the reward variant. In the punishment variant, the formula is [(E′ + G′] − (F′ + H′)] for five blocks of trials added to get a total net score.

MATERIALS

The computerized IGT progressive reward variant (A′B′C′D′) and progressive punishment variant (E′F′G′H′) were used. The progressive variant is slightly different from the original IGT because it exaggerates the future outcome, that is, it increases the magnitude of long-term rewards in the advantageous decks and the long-term punishments in the risky decks (Bechara et al., 2000b). Four types of instructions were used with suitable changes to the original (standard) IGT instructions (see Appendix).

PROCEDURE

Participants filled in demographic details in a form, were given an overview of the experiment, and provided informed consent. The study had the approval of a thesis committee (Research Progress Committee), a departmental committee, and an institute-level committee in charge of overseeing the post-graduate research program at the institute. Participants were tested individually in a laboratory and were assigned to one of the experimental conditions. Two IGT variants were presented in a counter-balanced design (i.e., reward variant followed by punishment variant or vice versa) with one of the four types of instructions (see **Figure 1**). Instructions were read before the first variant was presented. After finishing the first variant, a small break was given (5 min), and instructions were read for the second variant after which the second variant was presented. After completing both variants, participants were debriefed and thanked for their participation in the study.

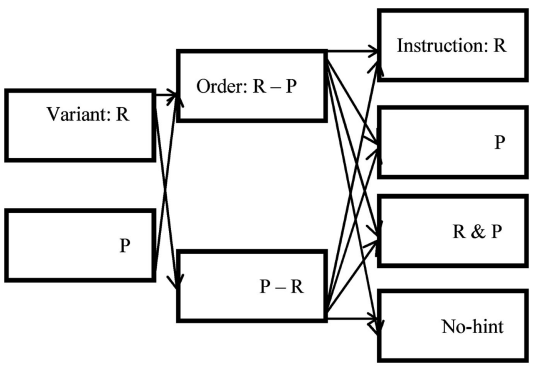

FIGURE 1 | Diagram showing variant type as a within-subjects factor (R = reward variant and P = punishment variant), order type (R–P = reward variant followed by punishment variant, P–R = punishment variant followed by reward variant), and instruction type (R = seek reward, P = avoid punishment, R and P = standard IGT instruction to seek reward and avoid punishment, No-hint = no-hint of reward or punishment) as between subjects factors ($n = 320$).

RESULTS

A mixed between-within subjects analysis of variance (ANOVA) was conducted to test the effects of order type (reward followed by punishment or punishment followed by reward variants), instruction type (seek reward, avoid punishment, standard, and no-hint) and IGT variant type (total net scores on reward and punishment variants). There was a significant within-subjects effect of variant type [Wilk's lambda = 0.96, $F(1, 312) = 14.66$, $p < 0.001$, partial eta squared = 0.04]. The interaction of order and variant types was significant [Wilk's lambda = 0.98, $F(1, 312) = 3.58$, $p < 0.05$, partial eta squared = 0.02; see **Figure 2**]. There was a significant interaction between instruction type and variant type [Wilk's lambda = 0.97, $F(3, 312) = 3.58$, $p < 0.05$, partial eta squared = 0.03; see **Figure 3**]. A Tukey's honestly significant difference (HSD) *post hoc* test showed that the instructions to seek reward had resulted in significantly higher IGT net scores compared to the standard IGT instructions ($p < 0.05$). A two-tailed binomial test showed that the number of participants making more advantageous decisions in the punishment variant than in the reward variant was greater irrespective of order or instruction type ($p < 0.001$; see **Table 1**).

DISCUSSION

Contrary to SMH postulations (Bechara et al., 2002), foresighted decision making varied across the reward and punishment variants of the IGT. An inability to make equally foresighted decisions in the two variants indicate that IGT decision making is affected by variant type (i.e., by the immediate reward or punishment frame of a decision). The impression that normal healthy adults make foresighted decisions irrespective of the variant type might be the effect of the variant, which is risk aversion in the reward variant and risk seeking in the punishment variant, masked by how the decision making in the variants is analyzed and reported (i.e., by judging impairment in the two variants using unequal cut-off scores). In an earlier study, positive and negative frame introduced prior to the reward variant of the IGT led to a frame-appropriate response (i.e., positive frame resulting in risk aversion and negative frame

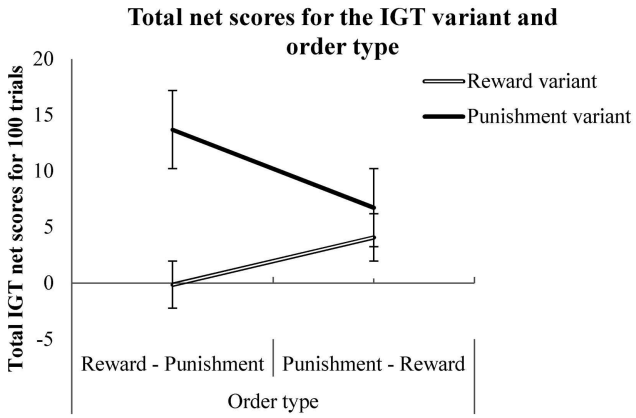

FIGURE 2 | Total net scores on the reward and the punishment variants (within-subjects) with the order of task presentation (between subjects). Error bars represent standard error.

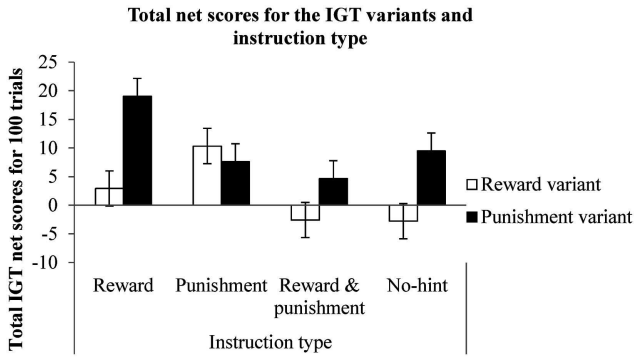

FIGURE 3 | Total net scores on the reward and the punishment variants (within-subjects) and the type of instructions (between subjects). Error bars represent standard error.

resulting in risk seeking) which was attributed to a spontaneous or an automatic process (Franken et al., 2006).

Consistent with the framing effect explanation for long-term decision making in the IGT, the order in which the variants were presented had an effect on the long-term advantageous decision making. It was difficult to examine on-the-surface differences between the two variants from the results of the previous studies due to an absence of a counter-balanced presentation of the two variants (e.g., Bechara et al., 2000b, 2002; Verdejo-Garcia et al., 2006) or an absence of a comparable healthy control group (Must et al., 2006, 2007). The present results point out a difference in long-term decision making in the reward and punishment variants, ruling out methodological issues.

The results showed that the alteration of reward and punishment sensitivity via task instruction had an effect on long-term decision making in the two variants. Uni-directional instructions (i.e., those that differentiated between reward and punishment) resulted in greater long-term decision making compared to the bi-directional standard instructions (i.e., those that had an indifference toward reward and punishment). This result might explain why standard instructions in the reward variant are known to encourage risk/loss avoidance more than they encourage reward-seeking (Balodis et al., 2006). It is possible that due to a positive frame imposed by the reward variant only the part of the standard instructions that directs the decision maker to avoid punishments is attended in the reward variant. In line with this assertion, it was found that delineating between the positive and negative frames of the standard instructions resulted in higher long-term decision making than the standard instructions that fail to differentiate between reward and punishment (Krawitz et al., 2010). In speculation, the right hemispheric dominance observed in the reward variant of the IGT (e.g., Bechara et al., 2000a; Manes et al., 2002; Clark et al., 2003; Bolla et al., 2004; Bark et al., 2005) might be indicative of a sensitivity to punishment and risk aversion because the right hemisphere is sensitive to negative affect (Sutton and Davidson, 1997; Davidson, 2004) and associated with risk aversion (Drake, 1985, 2002; Drake and Ulrich, 1992). Future studies could examine the right hemispheric dominance in the reward variant to determine if it indicates risk aversion or loss aversion and whether the punishment variant shows similar hemispheric activity.

The on-the-surface difference of greater long-term advantageous decision making in the punishment variant observed in the original study (Bechara et al., 2002) had led to the present investigation. As suspected, the number of participants making more long-term advantageous decisions in the punishment variant was higher (more than 60%) than in the reward variant. The results point out a difference in long-term decision making in the reward and punishment variants, contradicting the claim that IGT decision making is immune to reward and punishment orientation (Bechara et al., 1994, 2000b). The role of rewards and punishments has been a contentious issue in IGT studies. For example, contrary to the SMH-IGT assumption, the learning of rewards and punishments (Rolls et al., 1994), knowledge of rewards and punishments (Maia and McClelland, 2004), immediate rewards and punishments (van den Bos et al., 2006), and frequency of immediate rewards and punishments (Chiu and Lin, 2007; Lin et al., 2007; Chiu et al., 2008) are believed to confound long-term decision making in the reward variant of the IGT, weakening the assertion that IGT decision making is immune to reward and punishment sensitivity. The present results obtained from comparing both the variants of the IGT suggest that reward and punishment has an effect on long-term decision making in the IGT in the form of the variant type (reward and punishment), order type (reward followed by punishment and vice versa), and instruction type (either approach reward or avoid punishment, and approach reward while avoiding punishment).

There was evidence from the psychology literature that punishment or negative stimuli is potent (Kanhouse and Hanson, 1972), processed preferentially (Hansen and Hansen, 1988; Pratto and John, 1991; Lane et al., 1997), produces a strengthened response on the cognitive, emotional, and physiological levels (Taylor, 1991), and results in a stronger motivation (Taylor, 1991; Cacioppo et al., 1999) than reward or positive stimuli. It had been pointed out in the behavioral decision making literature that reward–punishment are unequally valued and have an asymmetrical influence (Tversky and Kahneman, 1981, 1991). Incorporating other relevant findings from behavioral studies such as temporal discounting, a preference for immediate reward over delayed ones (Ainslie, 1975), myopic loss aversion, an over-sensitivity to losses combined with shortsightedness (Benartzi and Thaler, 1995), preference based on frequency of reward (Loewenstein and Prelec, 1992), and on punishment (Bateman et al., 2007), will add valuable insights to a developing field of decision neuroscience.

The results underscore the role of socio-economic and cultural factors in understanding decision making in the IGT. Inconsistent with the IGT assumptions, frequencies of immediate reward and punishment rather than the inter-temporal nature of choices were determinants of IGT decision making in Taiwan (Chiu and Lin, 2007, Lin et al., 2007; Chiu et al., 2008), Iran (Ekhtiari et al., 2009), and Brazil (Bakos et al., 2010). While it is assumed that risk is perceived in terms of inter-temporality and risky decision making is manifested in the tradeoff between an immediate versus a delayed outcome (irrespective of reward or punishment as an outcome) in the IGT, socio-economic, and cultural differences in the IGT suggest an alternative definition of risk and risky decision making in

Table 1 | Mean and standard deviations of total net scores in the two variants by order ($n = 160$; male = 80) and instruction types ($n = 40$; male = 20).

Order type	Instruction type	Total net scores on reward variant	Total net scores on punishment variant
Reward–punishment variant	Seek reward	−01.85 (27.08)	29.10 (32.05)
	Avoid punishment	12.73 (27.09)	11.50 (36.44)
	Standard IGT	−07.35 (20.37)	03.20 (37.17)
	No-hint	−04.05 (24.43)	11.00 (23.70)
	Total	−00.13 (25.83)	13.70 (33.83)
Punishment–reward variant	Seek reward	07.70 (33.76)	09.00 (37.61)
	Avoid punishment	07.95 (26.22)	03.80 (21.65)
	Standard IGT	02.20 (26.34)	06.15 (30.73)
	No-hint	−01.50 (19.77)	08.00 (19.60)
	Total	04.09 (27.02)	06.74 (28.14)

the IGT. When socio-economic and cultural differences are investigated as a part of the decision neuroscience studies, it would benefit areas such as cultural neuroscience, and social neuroscience, by helping us understand the link between culture-specific decision making behavior and brain functioning.

The results pointed out a "negativity bias" in IGT decision making. Is it easier to make long-term advantageous decisions when the predominant outcome of every choice is a "loss"? Future investigations could examine the reason for the pronounced effect of a loss frame that instigates risk taking than of a gain frame that triggers risk aversion. In a task that is different from the IGT risk aversion was observed to be detrimental to long-term advantageous decision making (Shiv et al., 2005), whereas in the IGT (reward variant), risk aversion is necessary for long-term advantageous decision making (Balodis et al., 2006; Franken et al., 2006). Until now, the two variants have never been compared to test risk aversion in the reward variant and risk seeking in the punishment variant. Future studies could compare the two variants to test whether a pronounced effect of the punishment variant and risk seeking is specific to a socio-economic and cultural context. The methodology problem of counterbalancing the presentation of variants that occurred in earlier studies was addressed in this study, but the results need to be interpreted considering the limitation that the participants did not play using real money, which could be an important factor when comparing risk taking in the reward and punishment variants of IGT.

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APPENDIX

Four types of instructions were used in the study: standard (1a and 1b), seek reward (2), avoid punishment (3), and no-hint (4a and 4b) instructions.

1a. Standard instructions, reward variant: "In front of you on the screen, there are four decks of cards: A′, B′, C′, and D′. When we begin the game, I want you to select one card at a time by clicking on a card from any deck. Each time you select a card, the computer will tell you that you won some money. I do not know how much money you will win. You will find this out as you go along. Every time you win, the green bar at the top of the screen gets bigger. Every so often, when you click on a card, the computer will tell you that you won some money as usual, but it will also say that you lost some money as well. I do not know when you will lose or by how much. You will find out as you go along. Every time you lose, the green bar at the top of the screen gets smaller. You are absolutely free to switch from one deck to another at any time, and as often as you wish. *The goal of the game is to win as much money as possible and to avoid losing as much money as possible.* You would not know when the game will end. Simply keep on playing until the computer stops. You will have $2,000 of credit, shown by the green bar, at the start of the game. The only hint I can give you, which is the most important thing to note, is this: Out of these four decks of cards, some are worse than others. To win, you should try to stay away from bad decks. No matter how much you find yourself losing, you can still win the game if you avoid the bad decks. Moreover, the computer does not change the position of the decks once the game begins. It does not make you lose at random, or make you lose money based on the last card you picked."

1b. Standard instructions, punishment variant: "In front of you on the screen, there are four decks of cards: E′, F′, G′, and H′. When we begin the game, I want you to select one card at a time by clicking on a card from any deck. Each time you select a card, the computer will tell you that you lost some money. I do not know how much money you will lose. You will find this out as you go along. Every time you lose, the green bar at the top of the screen gets smaller. Every so often, when you click on a card, the computer will tell you that you lost some money as usual, but it will say that you gained some money as well. I do not know when you will gain or by how much. You will find out as you go along. Every time you gain some money, the green bar at the top of the screen gets bigger. You are absolutely free to switch from one deck to the other at any time, and as often as you wish. *The goal of the game is to avoid losing as much money as possible and to win as much money as possible.* You would not know when the game will end. Simply keep on playing until the computer stops. You will have $2,000 of credit, shown by the green bar, at the start of the game. The only hint I can give you, which is the most important thing to note, is this: Out of these four decks of cards, some are better than others. To win, you should try to choose from the good decks. No matter how much you find yourself losing, you can still win the game if you choose from the good decks. Moreover, the computer does not change the position of the decks once the game begins. It does not make you win or lose at random, or make you win or lose money based on the last card you picked."

2. Seek reward instructions: Same as in the standard instructions, reward variant, except that the bold text is now "*The goal of the game is to win as much money as possible.*"

3. Avoid punishment instructions: Same as in the standard instructions, punishment variant, except that the bold text is now "*The goal of the game is to avoid losing as much money as possible.*"

4a. No-hint instructions, reward variant: "In front of you on the screen, there are four decks of cards: A′, B′, C′, and D′. When we begin the game, I want you to select one card at a time by clicking on a card from any of these decks. Sometimes you will win points, and sometimes you will lose points. You are absolutely free to switch from one deck to another at any time, and as often as you wish. You would not know when the game will end. Simply keep on playing until the computer stops. You will have $2,000 of credit, shown by the green bar, at the start of the game. Moreover, the computer does not change the position of the decks once the game begins. It does not make you lose at random, or make you lose money based on the last card you picked."

4b. No-hint instructions, punishment variant: "In front of you on the screen, there are four decks of cards: E′, F′, G′, and H′. When we begin the game, I want you to select one card at a time by clicking on a card from any of these decks. Sometimes you will win points and sometimes you will lose points. You are absolutely free to switch from one deck to the other at any time, and as often as you wish. You would not know when the game will end. Simply keep on playing until the computer stops. You will have $2,000 of credit, shown by the green bar, at the start of the game. Moreover, the computer does not change the position of the decks once the game begins. It does not make you lose at random, or make you lose money based on the last card you picked."

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Aversive Pavlovian responses affect human instrumental motor performance

***Francesco Rigoli*[1,2]*, *Enea Francesco Pavone*[3,4] *and Giovanni Pezzulo*[2,5]**

[1] *Università di Siena, Siena, Italy*
[2] *Istituto di Scienze e Tecnologie della Cognizione, Consiglio Nazionale delle Ricerche, Roma, Italy*
[3] *Università di Roma "La Sapienza," Roma, Italy*
[4] *Fondazione Santa Lucia Istituto Di Ricovero e Cura a Carattere Scientifico, Roma, Italy*
[5] *Istituto di Linguistica Computazionale "Antonio Zampolli," Consiglio Nazionale delle Ricerche, Pisa, Italy*

Edited by:
Ben Seymour, University of Osaka, Japan

Reviewed by:
Jean-Claude Dreher, Centre National de la Recherche Scientifique, France
Raymond J. Dolan, University College London, UK

****Correspondence:***
Francesco Rigoli, Università di Siena, via Banchi di Sotto 55, 53100 Siena, Italy.
e-mail: francesco.rigoli@istc.cnr.it

In neuroscience and psychology, an influential perspective distinguishes between two kinds of behavioral control: instrumental (habitual and goal-directed) and Pavlovian. Understanding the instrumental-Pavlovian interaction is fundamental for the comprehension of decision-making. Animal studies (as those using the negative auto-maintenance paradigm), have demonstrated that Pavlovian mechanisms can have maladaptive effects on instrumental performance. However, evidence for a similar effect in humans is scarce. In addition, the mechanisms modulating the impact of Pavlovian responses on instrumental performance are largely unknown, both in human and non-human animals. The present paper describes a behavioral experiment investigating the effects of Pavlovian conditioned responses on performance in humans, focusing on the aversive domain. Results showed that Pavlovian responses influenced human performance, and, similar to animal studies, could have maladaptive effects. In particular, Pavlovian responses either impaired or increased performance depending on modulator variables such as threat distance, task controllability, punishment history, amount of training, and explicit punishment expectancy. Overall, these findings help elucidating the computational mechanisms underlying the instrumental-Pavlovian interaction, which might be at the base of apparently irrational phenomena in economics, social behavior, and psychopathology.

Keywords: controllability, goal-directed, habitual, Pavlovian, reinforcement learning

INTRODUCTION

In psychology and neuroscience, an influential perspective (the multicontroller framework) views human and animal behavior as the result of the interaction among instrumental (goal-directed and habitual) and Pavlovian systems (Mackintosh, 1983; Balleine and Dickinson, 1998; Daw et al., 2005; Dayan and Seymour, 2008; Balleine and O'Doherty, 2009). Contrary to instrumental controllers, which learn novel actions guided by reward maximization (Daw et al., 2005; Pezzulo and Castelfranchi, 2009; Pezzulo and Rigoli, 2011; Solway and Botvinick, 2012), the Pavlovian system associates hard-wired reactions to unconditioned or conditioned stimuli (Mackintosh, 1983; Dayan and Seymour, 2008). The instrumental-Pavlovian interaction has been studied both in animals (Estes and Skinner, 1941; Rescorla and Solomon, 1967; Overmier et al., 1971; Dickinson and Pearce, 1977; Colwill and Rescorla, 1988; Holland, 2004) and, more recently, in humans (Bray et al., 2008; Talmi et al., 2008; Huys et al., 2011). The most widely used paradigms are Pavlovian-instrumental transfer (PIT) and conditioned suppression. These paradigms have shown that Pavlovian stimuli influence both choice and vigor of instrumental behavior. For instance, in the Bray et al.'s (2008) study, the presence of an appetitive Pavlovian stimulus led participants to choose items previously associated with that stimulus. The most plausible explanation of this finding is that Pavlovian stimuli biased the items' value. From this and similar studies, it emerges that Pavlovian mechanisms influence goal values, while it remains unclear whether they can also influence the correct execution of an adaptive instrumental action. In relation to this, animal studies have demonstrated that Pavlovian responses can cause misbehavior, namely a paradoxical negative effect on animal's performance (Breland and Breland, 1966; Morse et al., 1967; Brown and Jenkins, 1968; Williams and Williams, 1969; Mackintosh, 1983; Hershberger, 1986). For example, in the negative auto-maintenance paradigm (Williams and Williams, 1969), pigeons were trained with a light repeatedly paired with food. As a consequence of the food-light association learning, these animals exhibited a conditioned response of pecking the light when it appeared. Crucially, this response did not have any instrumental consequences in this phase. Afterward, in the test phase, the light appeared for some trials, and food was given to pigeons when they abstained from pecking the light. Surprisingly, pigeons continued to exhibit the pecking response, although they gained less reward. This result was interpreted as the activation of the innate Pavlovian response of approaching food-related stimuli, at the expense of a more efficient instrumental action. On the basis of this and similar evidence, it has been proposed that flexible instrumental responses can be activated together with rigid Pavlovian ones. In such circumstances, Pavlovian responses are adaptive when they are compatible with

instrumental behavior. Alternatively, namely when they go in the opposite direction, Pavlovian responses are maladaptive (Dayan et al., 2006).

However, to date, the mechanisms underlying the Pavlovian influence on instrumental performance are largely unknown. This is particularly true for humans, in relation to whom evidence in favor of maladaptive Pavlovian effects on performance is scarce (Guitart-Masip et al., 2011).

THE PRESENT STUDY

The general aim of the present study was to analyze the influence of Pavlovian responses on instrumental motor performance in humans. Linked to this, we aimed to test whether, and in which conditions, it was possible to detect a maladaptive effect. We focused on the *aversive domain*, a condition widely used in the animal literature (Morse et al., 1967).

A first specific aim of the study was to investigate the role of three variables as possible modulators of the Pavlovian influence on performance:

(1) Temporal threat distance (TTD): Contemporary animal models consider the spatial and TTDs as modulating defensive behavior (Fanselow and Lester, 1988; Blanchard and Blanchard, 1989; McNaughton and Corr, 2004). In line with these models, when a threat is close (rather than distant), the Pavlovian activation could increase and impair performance.
(2) Motivational Value (MV): This variable depends on the past punishment history associated with a context. It is plausible that the amount of past punishment influences both the Pavlovian value of associated stimuli and the value of the goal of avoiding the punishment in the future. In other words, many punishments in the past could increase Pavlovian activation, which in turn could impair performance. At the same time, many punishments in the past could increase the goal-directed motivation towards safety, improving performance.
(3) Controllability (CON): This variable corresponds to the difficulty of a task. More specifically, CON can be defined as the probability of achieving an outcome associated to a positive value through instrumental behavior (Huys and Dayan, 2009). Many studies, related to learned-helplessness, have described the effects of CON (Mineka and Hendersen, 1985; Maier and Watkins, 2005). Experimental findings suggest that CON is inversely correlated with the level of conditioned fear response. For example, rats showed a stronger fear response in front of uncontrollable shocks than in front of controllable ones (Mineka et al., 1984). In relation to the present study, it is possible that low CON increases Pavlovian activation, which in turn could impair performance.

A second specific aim of the study was to investigate whether the Pavlovian system exerts its influence on performance even without explicit threat expectancy. A similar issue has been investigated with respect to physiological Pavlovian responses, such as skin conductance. Evidence indicates that, at least after a certain amount of learning, a conditioned skin conductance response can be detected even without explicit threat expectancy (Schell et al., 1991; Lipp and Edwards, 2002). However, to date, the role of punishment expectancy as a modulator of Pavlovian influences on behavior is unknown. In line with skin conductance experiments, we hypothesized an influence of the Pavlovian system on performance even without explicit threat expectancy.

A third specific aim of the study was to investigate the differential Pavlovian impact on goal-directed and habitual controllers. Some theoretical proposals have argued that Pavlovian responses mostly influence the goal-directed system (Loewenstein and O'Donoghue, 2004), whereas others assert a greater influence on a habitual system (Holland, 2004; Dayan et al., 2006).

In the present paper, we describe a behavioral experiment in which we analyzed human performance in a sensorimotor instrumental task, with the aim of investigating the influence of Pavlovian responses on instrumental performance. In the task, we compared two different conditions, one in which a cue (CS+) signaled that a mistake was punished by the delivery of an electric shock, and one in which another cue (CS−) signaled that a mistake was not punished. We reasoned that, in the first condition, both the Pavlovian and the instrumental controllers should have been active, whereas, in the second one, only the latter should have. By comparing the two conditions, and manipulating also the putative modulator variables, the effect of Pavlovian mechanisms on instrumental performance should have emerged.

MATERIALS AND METHODS

PARTICIPANTS

Thirty-eight volunteers (17 males and 21 females; mean age = 25 years, SD = 4.4) were recruited through the participant pool of the University of Rome "La Sapienza." The study was approved by the Ethics Committee of the Institute of Cognitive Sciences and Technologies of the Italian National Research Council.

TASK DESCRIPTION

Participants sat in front of a computer black screen for a task composed of 240 trials (see **Figure 1**). At every trial, a colored open circle appeared in the center of the screen. The circle was red (CS+ condition) for half of the trials and yellow (CS− condition) for the other half, with random order (CS+ and CS− colors were counterbalanced across subjects). After 2 s, a ball of the same color of the circle appeared in the middle of one of the four sides of the screen and moved toward the opposite side, passing through the circle. The velocity of the ball varied randomly trial-by-trial on two levels (Fast, Slow). Participants had to press a button with the index finger of the right hand when the ball was in the circle. During both blocks 1 and 2 (80 trials each), participants either received an electric shock (in CS+ condition) or not (in CS− condition) when making an error (i.e., they either pressed too slow or too fast). The shock was delivered to the same finger the subjects used to press, that is to the index finger of the right hand, and to the medium finger of the same hand. In block 3 (80 trials), no participants received an electric shock, ever. At the beginning of block 3, participants were informed of the absence of shock delivery.

Plausibly, participants had the goal of winning at every trial. However, during trials in which mistakes were punished with shock, the goal of winning reasonably had an even stronger value.

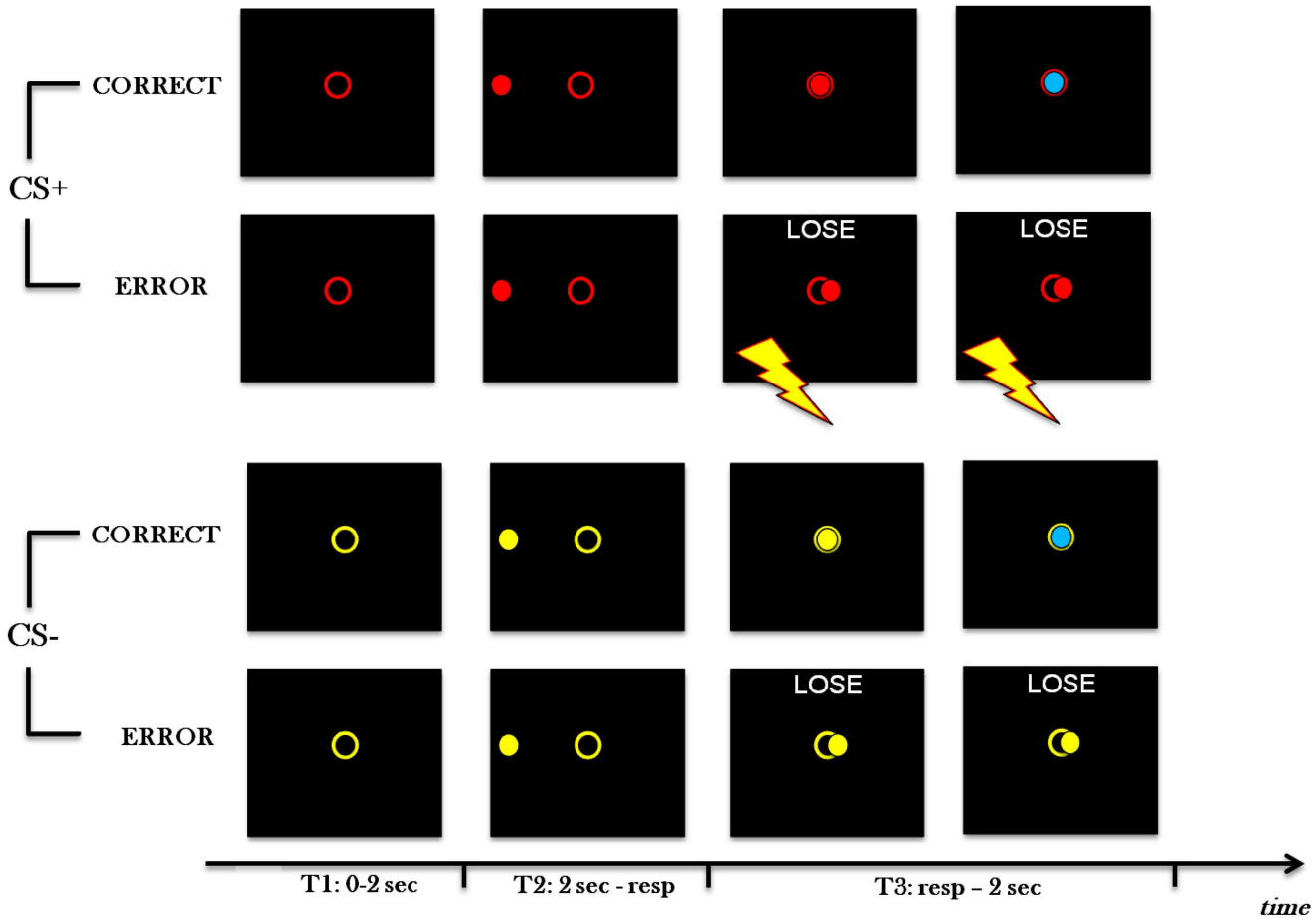

FIGURE 1 | Experimental paradigm. Four types of trials of Block 1 and 2 are shown, in which red is CS+ and yellow is CS−. From the top, the first example is with CS+ and a correct response; the second one is with CS+ and an error; the third one is with CS− and a correct response; the fourth one is with CS− and an error. At the beginning of each trial (T1), a colored open circle is presented in the center of the screen. After 2 s (T2), a ball appears in the center of one side of the screen and moves toward the opposite side, passing through the circle. Velocity varies randomly trial-by-trial on two levels. If the participant pushes the button at the right time (T3, first and third examples), and keeps it pressed for 1 s, the ball turns blue and, after a further second, a new trial begins. If the participant presses the button too fast or too slow (T3, second and forth examples), a negative feedback is displayed for 2 s, then a new trial begins. Furthermore, in CS+ conditions (second example), immediately after a mistake, an electric shock is delivered to the index finger that is used to press, and to the medium finger of the same hand. Electric shock lasts 500 ms. Contrary to Block 1 and 2, in Block 3 shock is never delivered with CS+.

A first possibility was that performance was proportional to instrumental value, hence that it was better in CS+ than CS−. Although this hypothesis is in line with some findings (Hull, 1943; Blake et al., 2002; Pleger et al., 2008), other evidence is at odds with it (Mackintosh, 1983; Dayan and Seymour, 2008; Guitart-Masip et al., 2011). A second possibility was that, in CS+, both the instrumental and the Pavlovian systems were activated by shock threat. Instrumental and Pavlovian activation would have an opposite effect on performance, the former enhancing it, the latter impairing it.

In order to operationalize one of the putative modulator variables, namely TTD, we manipulated the ball velocity on two levels (see Discussion for the implications of this procedure). The reason why velocity and TTD are inherently associated is that, in fast trials, participants expected the threat to be close in time, and vice versa in slow trials. This was aimed at testing whether, in line with the hypothesized role of TTD, the positive instrumental effects on performance emerged in slow trials, and the negative Pavlovian effects emerged in fast trials. We hypothesized velocity to be associated also with two other putative modulator variables, namely CON (i.e., in average we expected a better performance in slow trials than fast trials) and MV (i.e., in average we expected more shocks in fast CS+ trials than slow CS+ trials). To disentangle the role of TTD, CON, and MV, we planned a between-subjects analysis and a trial-by-trial analysis, in which each variable contribution could be separated from the others.

In addition, we investigated whether the Pavlovian system exerted its influence on performance even without explicit threat expectancy. To this aim, we studied performance also in extinction, namely in a third block where shock was never delivered and participants were informed of this.

Finally, we investigated whether the Pavlovian system differentially impacted on goal-directed and habitual controllers. Although goal-directed and habitual control coexist in most contexts (Daw et al., 2005; Wunderlich et al., 2012), research has shown that the relative strength of the two systems depends on the condition. Specifically, habitual control increases with experience (Daw et al., 2005) and performance in simple motor tasks increases when habitual control grows (Doyon et al., 2003). Based on these considerations, we analyzed two blocks of trials, hypothesizing that Block 1 was mostly guided by goal-directed mechanisms, whereas Block 2 by habitual ones. In order to verify this hypothesis, we tested whether performance increased in Block 2 compared to Block 1 (see Results).

APPARATUS AND MATERIALS

The experiment was conducted using E-Prime 1.2 software on a computer running Microsoft Windows. Participants sat 80 cm from a 21″ screen. Electrical pain stimulation was controlled and delivered by a Laika Excel Sport Stimulator, approved for clinical use.

STIMULI

The screen was black. The open circle in the center of the screen had a 1.8 cm radius, the ball was a filled circle of 0.7 cm radius. The circle and the ball were either red or yellow, varying randomly across trials. The velocity of the ball varied randomly on four levels, covering 0.3 cm every 9, 10, 13, and 15 ms (corresponding to velocity 1–4, respectively). The velocity levels were chosen on the base of a preliminary investigation conducted through a pilot study. Different levels of velocity were aggregated in two groups (velocity 1 and 2 corresponded to Fast Velocity; velocity 3 and 4 corresponded to Slow Velocity).

PROCEDURE

Before starting the task, a silver-chloride electrode was fixed to the medium finger of participants' right hand, while a second electrode was fixed under an aluminum layer glued upon a button. While participants repeatedly pushed and released the button with the right hand index finger, the electric stimulation was delivered and they could perceive it when they pushed. Starting from a very low level, the shock intensity was raised until each participant indicated it as quite unpleasant, just under the pain threshold. This level was adopted as punishment in the first block. The shock intensity setting procedure was repeated after the first block, and this second level was adopted in the second block. After the first and second blocks, participants were asked to evaluate the average electric stimulation received with two visual analog scales (VAS), one for intensity and one for unpleasantness.

After the first shock intensity setting, participants were fully instructed about the task. Afterward, they completed one practice block of eight trials and then three experimental blocks of 80 trials each. The practice and the three experimental blocks were all identical except that shock was not delivered in the third experimental block. At every trial, the open colored circle appeared in the center of the screen. After 2 s, the ball appeared on one side of the screen and immediately moved toward the opposite side. In order to win the trial, participants had to press the button at the right time and to keep it pressed for 1 s. Once they did it, the ball become blue and disappeared, and, after 1 s, a new trial began. If participants made a mistake, a negative feedback statement appeared for 2 s. At the same time, with the exception of the third block, in trials with CS+, an electric stimulation lasting 500 ms was delivered through the two electrodes, one fixed to the medium finger and one under the button. Following the feedback statement, a new trial started immediately. If participants did not press the button in a trial, an error feedback was presented and the trial was repeated. If participants pressed at the right time but released the button too early, an error feedback was presented. We instructed participants to keep the button pressed to avoid that they used the strategy to press and release quickly the button. This strategy could have led to a performance decrease that was not due to Pavlovian mechanisms, but to the adoption of different strategies in CS+ and CS−. In average, trials in which participants released the button were three per subject (SD = 2). In the analyses presented in this paper, these trials were scored as winnings. In order to ascertain that this scoring procedure did not affect the results, we also performed the same ANOVA analyses considering these trials as errors, obtaining equivalent results.

Before the third block, participants were informed about the absence of shock delivery, and the electrodes were removed. This procedure was taken from a previous study (Lipp and Edwards, 2002), as it revealed to be more effective in enhancing participants' trust than instructions delivery only. Moreover, at the end of the experiment, we asked participants to rate their confidence on the absence of shock in the third block. This was done to double-check that participants fully trusted the instructions.

RESULTS

AGGREGATED WITHIN-SUBJECTS ANALYSIS

As a first analysis, we conducted a repeated-measures analysis of variance (ANOVA) on the aggregated data with three independent variables ($2 \times 3 \times 2$): Stimulus (CS+ or CS−), Block (first, second, or third), and Velocity (Slow or Fast). We first performed this analysis using the average distance from the target-circle as dependent variable (see **Table 1** for means and SD in the different conditions). Importantly, distance was scored as negative when participants pressed too early, and as positive when they pressed too late. This analysis revealed a main effect of Velocity [$F(1,37) = 56.41$, $p = 0.000$, $\eta_p^2 = 0.61$; in this and in all following analyses the threshold for statistical significance was set to 0.05]. In other words, participants pressed the button at a larger distance in Fast Velocity than in Slow Velocity. All other main effects were non-significant [main affect of Block: $F(2,37) = 0.26$, $p = 0.76$; main effect of Stimulus: $F(1,37) = 0.09$, $p = 0.76$]. In addition, a Block × Velocity interaction was found [$F(2,74) = 4.4$, $p = 0.016$, $\eta_p^2 = 0.12$]. All other interactions were non-significant [Stimulus-Block: $F(2,74) = 2.44$, $p = 0.09$; Stimulus-Velocity: $F(1,37) = 0.2$; $p = 0.96$; Velocity-Block-Stimulus: $F(2,74) = 2.47$; $p = 0.092$].

In a second aggregated repeated-measure ANOVA analysis, we used the same factors as before, and performance, namely the percentage of winnings aggregated for each subject, as dependent variable (see **Table 1** for means and SD in the different conditions). Main effects are shown in **Figure 2**. Results showed a main effect of Block [$F(2,37) = 28.26$, $p = 0.000$, $\eta_p^2 = 0.43$].

Table 1 | Means and SD of distance and performance relative to the experimental conditions.

Condition	Distance		Performance	
	Mean	SD	Mean	SD
CS+, B1, F	−9.6	19.9	26.9	14.9
CS−, B1, F	−8.7	18.0	31.7	15.7
CS+, B1, S	5.1	26.7	49.7	20.4
CS−, B1, S	9.8	19.6	46.4	18.0
CS+, B2, F	−6.0	13.2	34.3	13.9
CS−, B2, F	−5.0	11.6	39.1	16.0
CS+, B2, S	6.7	15.9	60.7	17.8
CS−, B2, S	5.0	13.1	54.1	18.0
CS+, B3, F	−7.6	10.9	37.4	16.3
CS−, B3, F	−8.2	10.4	40.1	11.4
CS+, B3, S	6.7	12.8	53.5	15.6
CS−, B3, S	5.1	11.2	56.0	16.1
CS+, B3, F: low performance	–	–	29.4	10.3
CS−, B3, F: low performance	–	–	36.5	10.3
CS+, B3, S: low performance	–	–	45.1	14.7
CS−, B3, S: low performance	–	–	48.4	15.7

Factors are: Stimulus (CS+, CS−), Block (Block 1: B1, Block 2: B2, Block 3: B3), Velocity (Fast: F, Slow: S).

Paired-sample T-tests comparing Block 2 and Block 3 against Block 1 were significant [Block 1 vs. Block 2: $T(37) = -6$, $p = 0.000$; Block 1 vs. Block 3: $T(37) = -6{,}3$, $p = 0.000$; significance threshold Bonferroni-corrected], in line with the idea that the task was more routinized in the second and third blocks compared to the first one. In addition, participants performed better with Slow than Fast Velocity [$F(1{,}37) = 91.65$, $p = 0.000$, $\eta_p^2 = 0.71$]. A main effect of Stimulus was not present [$F(1{,}37) = 0.59$, $p = 0.448$]. However, we found a significant Stimulus-Velocity interaction [$F(1{,}37) = 9.64$, $p = 0.004$, $\eta_p^2 = 0.2$]. All other interactions were not significant [Stimulus-Block, $F(2{,}74) = 1.1$, $p = 0.334$; Velocity-Block, $F(2{,}74) = 1.94$, $p = 0.152$; Velocity-Block-Stimulus, $F(2{,}74) = 2.04$, $p = 0.137$].

To investigate our hypotheses specifically, we conducted orthogonal planned comparisons using paired-samples T-tests comparing CS+ and CS− trials across other conditions. We had an *a priori* hypothesis that performance in CS+ condition was worse than CS− condition with Fast Velocity, and vice versa with Slow Velocity, along all blocks (using one-tailed T-tests). This hypothesis derived from the expected role of TTD, which corresponded to Velocity in our paradigm. Results of orthogonal planned comparisons (**Figure 3**; see **Table 1** for means and SD) confirmed that, in Blocks 1 and 2, performance was worse in CS+ compared to CS− condition with Fast Velocity [Block 1: $T(37) = -1.8$, $p = 0.04$, $r = 0.28$; Block 2: $T(37) = -2.5$, $p = 0.008$, $r = 0.38$]. This effect was not found in Block 3 [$T(37) = -1.08$, $p = 0.144$]. We found that performance was better in CS+ compared to CS− condition with Slow Velocity only in Block 2 [$T(37) = -1.96$, $p = 0.029$, $r = 0.31$], while we did not find such effect in the other blocks [Block 1: $T(37) = 1.18$, $p = 0.125$; Block 3: $T(37) = -1.01$, $p = 0.159$].

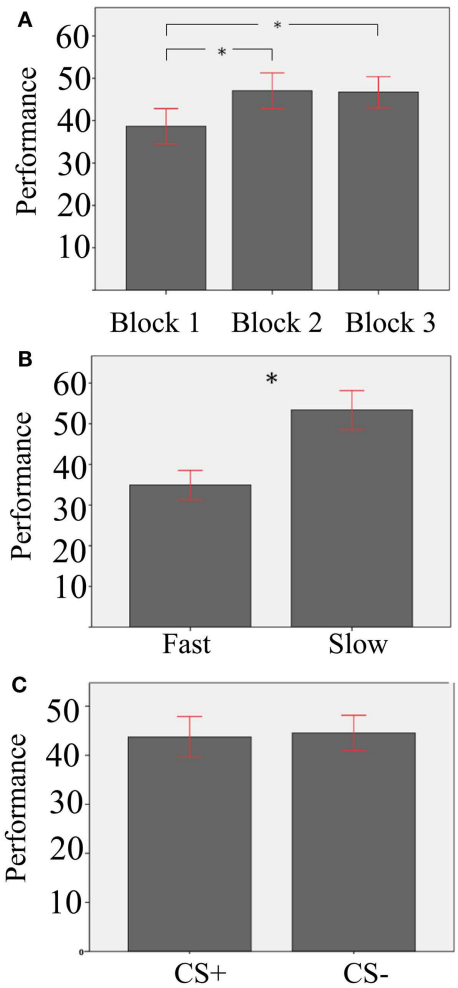

FIGURE 2 | Mean effects of the aggregated repeated-measures ANOVA with performance as dependent measure. (A) Effect of Block; asterisks indicate significant differences at a Bonferroni-corrected threshold of 0.05; **(B)** Effect of Velocity; the asterisk indicates a significant difference **(C)** non-significant effect of Stimulus. Error bars show the 95% confidence interval.

To further investigate the Pavlovian effect in the third block, we split the experimental sample in two subgroups using the median performance as a discriminative point (each group included 19 participants). Comparing CS+ to CS− condition in the third block for the Low-performance subgroup (see **Figure 3D**), performance was worse in the former than in the latter condition, with Fast Velocity [$T(18) = -2.2$, $p = 0.022$, $r = 0.46$]. No effect was found with Slow Velocity [$T(18) = 0.11$, $p = 0.26$].

CONTROL MEASURES

We collected some control measures to ascertain that the effects we found on performance were genuine. Perceived shock intensity in the first block was not significantly different from the one in the second block [paired-samples T-test: $T(37) = 0.77$, $p = 0.442$]. Similarly, the perceived shock unpleasantness did not significantly

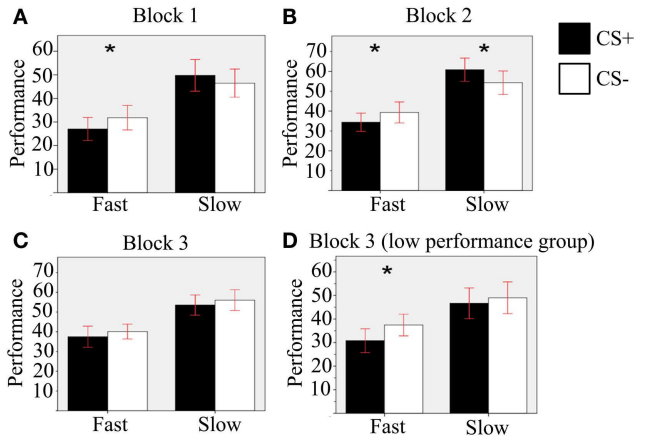

FIGURE 3 | Results of the orthogonal planned comparisons. Comparison between CS+ and CS− condition with Fast and Slow velocities in **(A)** the first block; **(B)** the second block; **(C)** the third block; **(D)** for the Low-performance subgroup, in the third block. Error bars show the 95% confidence interval. Asterisks indicate significant differences.

vary across the two blocks [$T(37) = 0.49$, $p = 0.631$]. Overall, participants trusted the instructions that they would not have received any shock in the third block. Indeed, the mean VAS score (in a 0–10 range) about the strength of the belief that they would have not received any shock in the third block was 9.5, and no scores were under 8.

A possible explanation of the observed impairing effect of CS+ on performance with Fast Velocity, compared to either a null effect (Block 1) or an increasing effect (Block 2) with Slow Velocity, might be that participants, in the CS+ condition, adopted different strategies with different velocities. In other words, they could have chosen to press as precisely as possible with Slow Velocity, since avoiding shock was relatively easier in this condition. On the contrary, since avoiding shock was relatively harder with Fast Velocity, they could have chosen not to employ much effort in responding, but, rather, to concentrate in releasing the button as soon as possible. Contrary to our hypothesis of the interaction between Pavlovian and instrumental controllers, this possibility is in line with the idea that behavior was only instrumental in the experiment. If this was true, we would have observed that participants, with Fast Velocity, released the button before they did with Slow Velocity. To rule out this possibility, we compared the time spent pressing the button in CS+ trials with Fast Velocity and with Slow Velocity, for Block 1 and Block 2. Results of this analysis demonstrated that participants did not release the button differentially with the two velocities in CS+ trials, obtaining the same amount of shock [paired-sample T-tests, one-tailed; Block 1: $T(37) = 0.43$, $p = 0.334$; Block 2: $T(37) = 0.54$, $p = 0.295$]. This result rules out the possibility that behavior, with Fast Velocity, was strategically aimed at minimizing shock by releasing the button quickly, at the expense of performance.

BETWEEN-SUBJECTS ANALYSIS

In the aggregated within-subjects analysis, we found a Stimulus-Velocity interaction effect on performance. As an inherent part of the paradigm, Velocity was associated with TTD. However, results showed that Velocity was also associated with CON (i.e., performance was better with Slow than Fast Velocity) and MV (i.e., participants collected more shocks with Fast Velocity than Slow Velocity). Therefore, from the previous analysis, it was not possible to assess the specific roles of TTD, CON, and MV as modulator variables of the effect of Pavlovian responses on instrumental performance. As a first way to test for an independent influence of CON, we devised a between-subjects analysis where we correlated the average performance with the difference in performance in CS− and CS+ conditions. The rationale of this analysis is that average performance can be considered as an index of each subject's CON on the task, which is independent of Velocity, since all subjects had the same amount of Fast and Slow Velocity trials. Therefore, by comparing participants with bad performance (corresponding to low CON) and participants with better performance (corresponding to high CON) in respect with the effect of Pavlovian responses on performance, it was possible to test for a specific role of CON, independently of the role of Velocity. This analysis (**Figure 4A**) revealed an inverse correlation between general performance and difference between performance with CS− and CS+ ($r = -0.36$, $p = 0.013$, one-tailed). However, given that average performance was calculated by adding CS+ and CS− performances, this measure was not independent of CS− minus CS+ performance. This can create concerns about the interpretation of the obtained correlation, since the two correlated variables were dependent ones. In general, the correlation between $x + y$ and $x - y$, where x and y are stochastic independent variables, should be zero when x and y have homogeneous variances. Therefore, to ensure that CS+ and CS− performances had homogeneous variances, we conducted a Levene's Test, which resulted not significant [$F(1,74) = 1.61$, $p = 0.2$]. This supported the idea that the correlation between average performance and performance with CS− minus CS+ was effective, and was not an artifact effect. In addition, the correlation between performance and performance with CS− minus CS+ was analyzed for each of the two velocities (**Figures 4B,C**, respectively). With Slow Velocity, this correlation was significant ($r = -0.32$, $p = 0.025$, one-tailed). With Fast Velocity, it was not significant ($r = -0.17$, $p = 0.14$, one-tailed). Levene's test was conducted also for the correlation with Slow Velocity, and it resulted not significant [$F(1,74) = 0.46$, $p = 0.5$].

TRIAL-BY-TRIAL ANALYSIS

As a second method to disentangle the roles of TTD, CON, and MV, we devised a model-based trial-by-trial statistical analysis (Daw, 2011; see Appendix for details). Indeed, although TTD, MV, and CON overlapped in the aggregated data, they could be disentangled if we consider data on a trial-by-trial basis. To do this, we operationalized TTD, MV, and CON in different ways (see Appendix for details). Specifically, CON varied according to the recent winning history; MV varied according to the recent shock history; and TTD was assumed to correspond to the Stimulus × Velocity interaction. By comparing the independent effects of TTD, MV, and CON on trial-by-trial performance (a dichotomous variable whose values were "correct response" and "incorrect response"), it was possible to disentangle the specific role of each variable

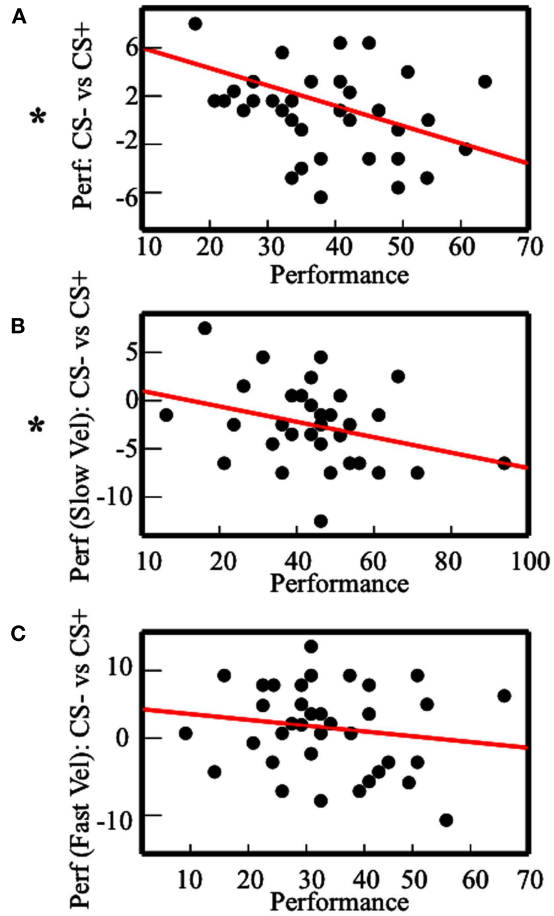

FIGURE 4 | Results of the between-subjects analysis. Correlation between the performance and the performance with CS− minus the performance with CS+. The plots describe the analysis with: **(A)** the average performance; **(B)** the performance with Slow Velocity; **(C)** the performance with Fast Velocity. Asterisks indicate significant Pearson-*r*.

in the modulation of the influence of Pavlovian responses on performance.

We used the ANOVA model as the baseline model, and we built a pool of alternative models including different combinations of the ANOVA elements plus MV and CON (see **Table 2**). Overall, the trial-by-trial model-based analysis revealed that the model implementing the ANOVA model plus MV performed better than other models in predicting performance on a trial-by-trial basis. In addition, it is important to note that adding MV to the ANOVA model did not affect the significance of the STIM × VEL parameters. Thus, the effect of TTD, operationalized as the STIM × VEL interaction, appeared not to be influenced by the trial-by-trial changes in MV and CON. In sum, TTD and MV, contrary to CON, appeared to be independent modulator variables of the Pavlovian effect on performance on a trial-by-trial basis.

DISCUSSION

The present study aimed to elucidate the Pavlovian-instrumental interaction in humans. Recent studies have investigated this issue, demonstrating that Pavlovian values influence instrumental behavior (Bray et al., 2008; Talmi et al., 2008; Huys et al., 2011). In particular, it has been shown that Pavlovian processes influence action and goal values. However, evidence in relation to a Pavlovian influence on instrumental performance is scarce. In other words, it is unclear whether and in which conditions Pavlovian responses facilitate, or interfere with, instrumental goals (Guitart-Masip et al., 2011). Following animal studies like the negative auto-maintenance paradigm (Williams and Williams, 1969), we aimed to investigate the Pavlovian influence on instrumental performance in humans, and the potential modulator variables of this influence.

To this aim, we studied human behavior in a simple sensorimotor task, comparing a condition in which a cue signaled that mistakes were punished with shock (CS+ condition) with a control condition in which a different cue signaled that mistakes were not punished (CS− condition). We studied different putative modulator variables of the Pavlovian impact on performance: amount of training, explicit shock expectancy, ball velocity (TTD), shock history (MV), and task difficulty (CON).

A first result of the within-subjects aggregated analysis indicated that Pavlovian stimuli did not have any effect on the distance (from the target-circle) at which participants pressed the button. However, the same analysis having performance as dependent variable revealed that, in Blocks 1 and 2, average performance was worse in CS+ than CS−with Fast Velocity. In the first part of the task (Block 1), performance with Slow Velocity was not different in CS+ and CS−, but, in the second part (Block 2), it was better in the former than in the latter. It is important to note that explicit shock expectancy was present in both Block 1 and Block 2. On the contrary, in the last part of the task (Block 3), shock was no more expected. In this condition, low average-performance participants (but not high-average performance ones) were worse in CS+ than CS−, with Fast Velocity.

A limit of the within-subjects aggregated analysis was that ball Velocity was associated with TTD, CON, and MV. Indeed, TTD was inherently associated with Velocity. In addition, participants performed better with Slow than Fast Velocity (CON), and received more shocks in Fast than Slow Velocity (MV). Therefore, the aggregated analysis did not allow us to detect the modulator independent contributes. To test for the independent roles of TTD, MV, and CON, we devised two methods: a between-subjects analysis and a trial-by-trial analysis. The between-subjects analysis showed that participants' average performance, depending on participants' CON, was correlated with the Pavlovian impairing effect. In other words, participants with bad performance, compared to participants with better performance, tended to perform worse in CS+ than CS− trials.

As a second method to disentangle the independent effects of the modulator variables, we conducted a trial-by-trial analysis. Indeed, TTD, MV, and CON could be operationalized in such a way that they varied independently on a trial-by-trial basis. This analysis showed that TTD and MV, contrary to CON, had independent effects on the Pavlovian influence on performance on a trial-by-trial basis. In particular, in relation to TTD, performance decreased with CS+ when the threat was nearest in time. In relation to MV, performance improved with CS+ after

Table 2 | Labels and equations of the models.

Model	LR	Formula	AIC	−LL
1	–	α	6826	6826
2	–	$\alpha+\beta\cdot\text{BLOCK}$	6824	6748
3	–	$\alpha+\beta\cdot\text{BLOCK}+\gamma\cdot\text{VEL}$	6612	6460
4	–	$\alpha+\beta\cdot\text{BLOCK}+\gamma\cdot\text{VEL}+\delta\cdot\text{STIM}$	6648	6420
5	–	$\alpha+\beta\cdot\text{BLOCK}+\gamma\cdot\text{VEL}+\delta\cdot\text{STIM}+\varepsilon\cdot\text{VEL}\cdot\text{STIM}$	6671	6367
6	0.1	$\alpha+\beta\cdot\text{BLOCK}+\gamma\cdot\text{VEL}+\zeta\cdot\text{MV}$	6636	6408
7	0.1	$\alpha+\beta\cdot\text{BLOCK}+\gamma\cdot\text{VEL}+\delta\cdot\text{STIM}+\zeta\cdot\text{MV}$	6624	6320
8	0.1	$\alpha+\beta\cdot\text{BLOCK}+\gamma\cdot\text{VEL}+\varepsilon\cdot\text{VEL}\cdot\text{STIM}+\zeta\cdot\text{MV}$	6616	6312
9	0.1	$\alpha+\beta\cdot\text{BLOCK}+\gamma\cdot\text{VEL}+\delta\cdot\text{STIM}+\varepsilon\cdot\text{VEL}\cdot\text{STIM}+\zeta\cdot\text{MV}$	6576	6196
10	0.4	$\alpha+\beta\cdot\text{BLOCK}+\gamma\cdot\text{VEL}+\zeta\cdot\text{MV}$	6631	6403
11	0.4	$\alpha+\beta\cdot\text{BLOCK}+\gamma\cdot\text{VEL}+\delta\cdot\text{STIM}+\zeta\cdot\text{MV}$	6660	6356
12	0.4	$\alpha+\beta\cdot\text{BLOCK}+\gamma\cdot\text{VEL}+\varepsilon\cdot\text{VEL}\cdot\text{STIM}+\zeta\cdot\text{MV}$	6621	6317
13	0.4	$\alpha+\beta\cdot\text{BLOCK}+\gamma\cdot\text{VEL}+\delta\cdot\text{STIM}+\varepsilon\cdot\text{VEL}\cdot\text{STIM}+\zeta\cdot\text{MV}$	6649	6269
14	0.7	$\alpha+\beta\cdot\text{BLOCK}+\gamma\cdot\text{VEL}+\zeta\cdot\text{MV}$	6633	6405
15	0.7	$\alpha+\beta\cdot\text{BLOCK}+\gamma\cdot\text{VEL}+\delta\cdot\text{STIM}+\zeta\cdot\text{MV}$	6671	6367
16	0.7	$\alpha+\beta\cdot\text{BLOCK}+\gamma\cdot\text{VEL}+\varepsilon\cdot\text{VEL}\cdot\text{STIM}+\zeta\cdot\text{MV}$	6640	6336
17	0.7	$\alpha+\beta\cdot\text{BLOCK}+\gamma\cdot\text{VEL}+\delta\cdot\text{STIM}+\varepsilon\cdot\text{VEL}\cdot\text{STIM}+\zeta\cdot\text{MV}$	6679	6299
18	1	$\alpha+\beta\cdot\text{BLOCK}+\gamma\cdot\text{VEL}+\zeta\cdot\text{MV}$	6640	6412
19	1	$\alpha+\beta\cdot\text{BLOCK}+\gamma\cdot\text{VEL}+\delta\cdot\text{STIM}+\zeta\cdot\text{MV}$	6679	6375
20	1	$\alpha+\beta\cdot\text{BLOCK}+\gamma\cdot\text{VEL}+\varepsilon\cdot\text{VEL}\cdot\text{STIM}+\zeta\cdot\text{MV}$	6657	6353
21	1	$\alpha+\beta\cdot\text{BLOCK}+\gamma\cdot\text{VEL}+\delta\cdot\text{STIM}+\varepsilon\cdot\text{VEL}\cdot\text{STIM}+\zeta\cdot\text{MV}$	6694	6314
22	0.1	$\alpha+\beta\cdot\text{BLOCK}+\gamma\cdot\text{VEL}+\eta\cdot\text{CON}\cdot\text{STIM}$	6648	6420
23	0.1	$\alpha+\beta\cdot\text{BLOCK}+\gamma\cdot\text{VEL}+\delta\cdot\text{STIM}+\eta\cdot\text{CON}\cdot\text{STIM}$	6683	6379
24	0.1	$\alpha+\beta\cdot\text{BLOCK}+\gamma\cdot\text{VEL}+\varepsilon\cdot\text{VEL}\cdot\text{STIM}+\eta\cdot\text{CON}\cdot\text{STIM}$	6685	6381
25	0.1	$\alpha+\beta\cdot\text{BLOCK}+\gamma\cdot\text{VEL}+\delta\cdot\text{STIM}+\varepsilon\cdot\text{VEL}\cdot\text{STIM}+\eta\cdot\text{CON}\cdot\text{STIM}$	6680	6300
26	0.4	$\alpha+\beta\cdot\text{BLOCK}+\gamma\cdot\text{VEL}+\eta\cdot\text{CON}\cdot\text{STIM}$	6647	6419
27	0.4	$\alpha+\beta\cdot\text{BLOCK}+\gamma\cdot\text{VEL}+\delta\cdot\text{STIM}+\eta\cdot\text{CON}\cdot\text{STIM}$	6674	6370
28	0.4	$\alpha+\beta\cdot\text{BLOCK}+\gamma\cdot\text{VEL}+\varepsilon\cdot\text{VEL}\cdot\text{STIM}+\eta\cdot\text{CON}\cdot\text{STIM}$	6679	6375
29	0.4	$\alpha+\beta\cdot\text{BLOCK}+\gamma\cdot\text{VEL}+\delta\cdot\text{STIM}+\varepsilon\cdot\text{VEL}\cdot\text{STIM}+\eta\cdot\text{CON}\cdot\text{STIM}$	6686	6306
30	0.7	$\alpha+\beta\cdot\text{BLOCK}+\gamma\cdot\text{VEL}+\eta\cdot\text{CON}\cdot\text{STIM}$	6643	6415
31	0.7	$\alpha+\beta\cdot\text{BLOCK}+\gamma\cdot\text{VEL}+\delta\cdot\text{STIM}+\eta\cdot\text{CON}\cdot\text{STIM}$	6675	6371
32	0.7	$\alpha+\beta\cdot\text{BLOCK}+\gamma\cdot\text{VEL}+\varepsilon\cdot\text{VEL}\cdot\text{STIM}+\eta\cdot\text{CON}\cdot\text{STIM}$	6672	6368
33	0.7	$\alpha+\beta\cdot\text{BLOCK}+\gamma\cdot\text{VEL}+\delta\cdot\text{STIM}+\varepsilon\cdot\text{VEL}\cdot\text{STIM}+\eta\cdot\text{CON}\cdot\text{STIM}$	6692	6312
34	1	$\alpha+\beta\cdot\text{BLOCK}+\gamma\cdot\text{VEL}+\eta\cdot\text{CON}\cdot\text{STIM}$	6642	6414
35	1	$\alpha+\beta\cdot\text{BLOCK}+\gamma\cdot\text{VEL}+\delta\cdot\text{STIM}+\eta\cdot\text{CON}\cdot\text{STIM}$	6679	6375
36	1	$\alpha+\beta\cdot\text{BLOCK}+\gamma\cdot\text{VEL}+\varepsilon\cdot\text{VEL}\cdot\text{STIM}+\eta\cdot\text{CON}\cdot\text{STIM}$	6669	6365
37	1	$\alpha+\beta\cdot\text{BLOCK}+\gamma\cdot\text{VEL}+\delta\cdot\text{STIM}+\varepsilon\cdot\text{VEL}\cdot\text{STIM}+\eta\cdot\text{CON}\cdot\text{STIM}$	6699	6319
38	0.1	$\alpha+\beta\cdot\text{BLOCK}+\gamma\cdot\text{VEL}+\delta\cdot\text{STIM}+\varepsilon\cdot\text{VEL}\cdot\text{STIM}+\zeta\cdot\text{MV}+\lambda\cdot\text{Shock}_{n-1}$	6590	6134
39	0.1	$\alpha+\beta\cdot\text{BLOCK}+\gamma\cdot\text{VEL}+\delta\cdot\text{STIM}+\varepsilon\cdot\text{VEL}\cdot\text{STIM}+\zeta\cdot\text{MV}+\mu\cdot\text{Outcome}_{n-1}$	6601	6145
40	0.1	$\alpha+\beta\cdot\text{BLOCK}+\gamma\cdot\text{VEL}+\delta\cdot\text{STIM}+\varepsilon\cdot\text{VEL}\cdot\text{STIM}+\zeta\cdot\text{MV}+\mu\cdot\text{Outcome}_{n-1}+\lambda\cdot\text{Shock}_{n-1}$	6657	6125

LR, learning rate of the model; AIC, Akaike information criterion; −LL, negative log-likelihood.

a shock had been collected in the previous CS+ trial. Overall, the between-subjects and the trial-by-trial analyses showed that TTD, CON, and MV had independent roles as modulator variables. However, these variables acted at different levels. Specifically, TTD and MV acted at a local level, since their influence was observed on a trial-by-trial basis. On the contrary, CON acted at a more global level. Indeed, its influence was observed at the between-subjects level only, suggesting that participants had a quite stable CON-related belief (independently of the recent success history), that modulated the Pavlovian impact on performance.

We interpret these results within a theoretical framework which views behavior as the output of the interaction between instrumental and Pavlovian controllers (Daw et al., 2005; Dayan and Seymour, 2008). According to this perspective, instrumental controllers select actions proportionally to their values, although each controller follows specific rules (Daw et al., 2005). In the present study, if only this process was active, performance should have

been better in CS+ than CS− condition. However, as animal studies have shown, in many cases behavior is not only instrumental. Rather, reactive hard-wired responses to rewards and punishments either impair or strengthen the instrumental action efficacy (Dayan and Seymour, 2008).

In line with this view, we interpret the performance impairment in CS+ respect to CS− condition with Fast Velocity as the Pavlovian maladaptive influence on instrumental performance. Indeed, with Fast Velocity, people performed worse when expecting shock than no-shock. Consequently, they avoided less shocks than they could (as confirmed also by the analysis of the time spent pressing), plausibly against their intentions. This finding suggests that, similarly to the negative auto-maintenance paradigm in animals (Williams and Williams, 1969), Pavlovian responses can have maladaptive effects in humans too.

Alternative explanations of these findings are related to the "choking under pressure effect," according to which people sometimes perform worse when facing high rewards and punishments. The "choking under pressure effect" has been given three different interpretations. The first one hypothesizes an inverted-U relationship between arousal and performance (Yerkes and Dodson, 1908; Neiss, 1988). The second one maintains that, in stressful situations, people choose to rely on controlled strategies during a task execution, with the idea that this choice is more advantageous compared to relying on more automatic mechanisms. However, this strategy actually would carry to performance decay, in line with studies showing that controlled strategies are less effective for highly practiced and automated tasks (Langer and Imber, 1979). Finally, a third interpretation of the "choking under pressure effect" maintains that stressful situations determine a narrowing of attention, which, in turn, would be detrimental for tasks requiring creativity and flexibility (Eisterbrook, 1959).

In general, the multicontroller framework is not incompatible with the standard interpretations of the "choking under pressure effect." However, we believe that, for understanding our results, the multicontroller framework should be preferred to these interpretations. The general reason is that, in the present paradigm, the state of "pressure" was specifically manipulated through Pavlovian stimuli presentation, rather than through other mechanisms, as in standard "choking under pressure" experiments. Therefore, the state of "pressure" was reasonably mediated by Pavlovian mechanisms, and behavior was reasonably influenced by Pavlovian responses. In respect to the first model of the "choking under pressure effect," it has been argued that the construct of arousal is quite ambiguous (Neiss, 1988). For example, it is not clear which arousal components would lead to performance increasing and decreasing. In addition, it is not clear how arousal is influenced by the environment, and which computational principles it follows. Therefore, we argue that referring to the multicontroller framework, whose features have been largely studied psychologically, neurally, and computationally, is more useful to interpret the present results. In respect to the second proposal related to the "choking under pressure effect" (Langer and Imber, 1979), this could have hypothesized that shock expectancy made participants rely on more controlled strategies, with maladaptive consequences. If this was true, we would have observed general performance decay with shock. On the contrary, decay was observed only with Fast Velocity, whereas performance increased with Slow Velocity (in the second block). This finding can hardly be reconciled with the idea that controlled strategies, triggered by shock, impaired performance. Finally, in relation to the third hypothesis on the "choking under pressure effect" (Eisterbrook, 1959), we argue that the present experimental task was very simple and repetitive, and distracters were absent. Therefore, the narrowing of attention, advocated by this hypothesis as responsible for performance decay under pressure, can hardly explain our observations.

The between-subjects and the trial-by-trial analyses showed that TTD, CON, and MV had independent roles in modulating the effects of Pavlovian responses on performance. Past research has indicated that temporal and spatial distances modulate aversive behavior (Fanselow and Lester, 1988; Blanchard and Blanchard, 1989). Therefore, in relation to the present study, TTD, which co-varied with ball velocity, reasonably modulated the Pavlovian influence on performance. However, ball velocity could have exerted its effect via other mechanisms. A possibility is that Velocity *per se*, rather than TTD, influenced the Pavlovian effect on performance. This possibility cannot be ruled out by the present experiment, and deserves further investigation.

The between-subjects analysis suggests that average performance, linked to participant's CON, inversely correlated with the impairing Pavlovian effect on performance. This is in line with evidence indicating that CON modulates Pavlovian activation. In particular, it has been shown that low CON increases fear conditioned responses (Mineka et al., 1984). The finding that the trial-by-trial analysis did not reveal any local effect of CON is apparently at odds with this interpretation. However, learned-helplessness studies suggest that CON is quite stable, and is not influenced by local performance changes (Mineka and Hendersen, 1985; Maier and Watkins, 2005). This could explain why CON effects could not be detected on a trial-by-trial basis, but emerged when comparing participants with different average performance.

Finally, the trial-by-trial analysis indicated an independent effect of MV. This variable depended on past shocks. We first hypothesized that MV impaired performance, by enhancing the Pavlovian maladaptive activation. Alternatively, MV could have improved performance, by increasing the value of the goal of avoiding the punishment. The trial-by-trial analysis, showing that performance increased in CS+ after a shock had been collected in the previous CS+ trial, supported the latter hypothesis.

We also tested whether Pavlovian effects on performance were detected even without explicit shock expectancy. With this regard, Pavlovian impairing effects with Fast Velocity emerged also in extinction, namely in a last block without shocks (in which participants knew about the new contingency). Noteworthy, this effect was found only in low average-performance participants. These results are in accordance with previous findings showing that the skin conductance conditioned response can be detected even without explicit shock expectancy (Schell et al., 1991; Lipp and Edwards, 2002). In relation to these and our findings, it is possible that two distinct processes, one model-based and the other model-free, as defined in reinforcement-learning literature (Sutton and Barto, 1998; Daw et al., 2005; Rigoli et al., 2011; Solway and Botvinick, 2012), are involved in Pavlovian learning. When the explicit belief about the stimulus-shock contingency is reversed

by verbal instructions, as in the third block, the model-based Pavlovian process would be quickly updated. On the contrary, the model-free process would not be affected by verbal instructions, and would continue to trigger directly a CR every time a CS+ appears. The fact that the maladaptive Pavlovian influence was found only in low average-performance participants could be due to the modulatory effect of CON (low average performance corresponded to low CON) on the model-free Pavlovian activation.

Another issue regards the differential Pavlovian impact on goal-directed and habitual mechanisms. The fact that performance improved in Block 2 and 3, compared to Block 1, allowed us to assume that, in Blocks 2 and 3, the habitual system was more active than in Block 1. The Pavlovian impairing effect with Fast Velocity emerged both in Blocks 1 and 2, associated to goal-directed and habitual mechanisms, respectively. On the contrary, the enhancing effect of CS+ on performance with Slow Velocity emerged in Block 2 only. A possible explanation of this evidence is that over-learned reactions, linked to habitual control, are immune to impairing Pavlovian effects in slow trials. Alternatively, CS+ could increase performance in over-learned tasks, contrary to non-over-learned ones, in slow trials. However, CON might be actually responsible for the differential Pavlovian effects on goal-directed and habitual mechanisms. Indeed, CON was lower in Block 1 than Block 2, since average performance increased along blocks.

In relation to the present results, an important aspect regards the specific nature of the CR, and the level at which it influenced instrumental performance. Following previous literature, three different hypotheses can be formulated, based on the idea of a conflict between an instrumental motor command and a co-occurring CR. The hypotheses differ with respect to the nature of the CR and the level of its influence. A first hypothesis is that, in line with neurobiological evidence (Butler et al., 2007), the CR corresponded to a specific motor response competing against a co-occurrent instrumental motor command. According to this interpretation, in the context of our experiment, the instrumental motor response of pressing the button at the right time could be impaired by a co-active specific CR of withdrawing the finger, associated with the painful shock delivered to the finger itself. The second hypothesis is that an aversive CS+ triggered a general motor inhibition reaction, leading to instrumental impairment (Gray, 1982; Crockett et al., 2009; Guitart-Masip et al., 2011). Finally, the third hypothesis is that a non-specific CR (e.g., trembling) impaired the precision of an instrumental motor command (Mobbs et al., 2009). The precision of a motor command can be defined as the noise of the actual behavior with respect to a planned motor command. In the context of our experiment, this noise could be inflated by a non-specific CR, leading to performance decrease. These three hypotheses make different predictions in respect to our experimental results. According to the first two hypotheses, it was expected that participants pressed at a larger distance to the target in CS+ than CS−. However, we did not find any Stimulus effect on distance, not even considering its interaction with Velocity or Block. This result is more consistent with the third hypothesis, postulating a non-specific CR, such as trembling, affecting instrumental motor precision.

A final aspect regards the associative relationships underlying conditioning in our experiment. Each trial included the following stimuli: the circle, the moving ball, and the visual feedback (plus the shock in some cases). The visual feedback and the shock worked as US and, in our analysis, we assumed that the circle worked as CS+. However, an alternative possibility is that the moving ball worked actually as CS+, whereas the circle worked as an occasion setter. Associative learning theories distinguish between CSs and occasion setters, which would follow different associative processes. In particular, CSs have a direct relationship with USs, whereas occasion setters determine the condition in which CSs are associated with USs (Holland, 1992). A limit of the paradigm we used is that it did not allow to ascertain whether either the circle or the moving ball worked as CS+. However, we argue that this limit does not hinder the present findings, since they are related to the effects of Pavlovian responses on performance. In other words, the CR influence on performance, modulated by the variables investigated, is not affected by the fact that the circle or the moving ball worked as CS+. However, future research should understand which CSs can produce CRs influencing instrumental performance. Another important aspect of the present study regards its generalizability. Indeed, the Pavlovian effects (and their modulators) found here could be related to the task used, which required a simple and precise motor execution. It is possible that Pavlovian mechanisms have maladaptive effects only in some kinds of task, whereas they might have neutral, or even positive, effects in other kinds. Further investigation is needed for the study of Pavlovian influence in other tasks and conditions.

THE NEUROBIOLOGY OF THE INTERACTION BETWEEN PAVLOVIAN AND INSTRUMENTAL CONTROLLERS

In this section, we describe the neurobiology of the Pavlovian-instrumental interaction and relate it to the present findings. Evidence suggests that different motivational systems (goal-directed, habitual, and Pavlovian) involve specific neural substrates (Balleine and Dickinson, 1998; Yin et al., 2008; Balleine and O'Doherty, 2009; Glascher et al., 2010; Guitart-Masip et al., 2011; Huys et al., 2011; Pezzulo and Rigoli, 2011; Simon and Daw, 2011; Wunderlich et al., 2012). The importance of studying the neural substrates of the interaction amongst controllers has been recently stressed (Balleine and O'Doherty, 2009; Bornstein and Daw, 2011), since these interactions are poorly understood, especially regarding the instrumental-Pavlovian one. In relation to this, research has mostly focused on the Pavlovian effects on action value and general motor reactivity.

With regard to action value, orbitofrontal cortex (Padoa-Schioppa and Assad, 2006), amygdala (Schoenbaum et al., 2003), and striatum (O'Doherty et al., 2004) have been shown to encode action values, although these structures are differentially recruited by the goal-directed and the habitual controllers (Pennartz et al., 2011; Wunderlich et al., 2012). At the same time, amygdala and ventral striatum have been shown to encode Pavlovian values (O'Doherty et al., 2004; Yin et al., 2008; Balleine and O'Doherty, 2009). In line with this evidence, recent findings suggest that amygdala and basal ganglia, where Pavlovian and instrumental value computations overlap, are crucial for Pavlovian-instrumental interactions (Bray et al., 2008; Talmi et al., 2008).

Other studies have focused on the Pavlovian effects on general motor reactivity (Gray, 1982; Crockett at al., 2009; Guitart-Masip et al., 2011). Dopamine and serotonin have been extensively reported as modulators of motivation and vigor (Niv et al., 2007; Boureau and Dayan, 2010). Recent studies have suggested that these neurotransmitters, particularly in the striatum, are responsible for excitatory and inhibitory Pavlovian effects on motor reactivity (Talmi et al., 2008; Crockett at al., 2009; Guitart-Masip et al., 2011).

In addition to action value and general motor reactivity, Pavlovian mechanisms might influence also other aspects of instrumental behavior, which should be considered by future research. For instance, Pavlovian and instrumental controllers might interact at specific motor levels, activating parallel motor neural processes. With this regard, the periaqueductal gray matter triggers automatic Pavlovian motor responses (Keay and Bandler, 2001), whereas cortical motor areas (the motor, pre-motor, and supplemental motor areas), together with basal ganglia, produce instrumental motor outputs (Balleine and Dickinson, 1998; Yin et al., 2008; Balleine and O'Doherty, 2009). A Pavlovian stimulus might activate specific motor outputs both in the periaqueductal gray matter and in instrumental motor areas.

A second underexplored possibility in relation to the Pavlovian-instrumental interaction is that Pavlovian mechanisms impact on the precision of a motor execution. The motor precision is partially independent of rapidity and motor reactivity. The present findings, showing an effect on precision and no effect on rapidity, suggest that Pavlovian stimuli can have a specific impact on the motor execution precision. At the neural level, neurotransmitters as dopamine, serotonin, and noradrenaline are known to modulate the executive processes, and they might impact on the motor execution precision (Niv et al., 2007; Boureau and Dayan, 2010). In addition, structures such as amygdala and striatum have modulatory effects on executive processes, and might also be involved in this context (Davis, 1992; Fanselow, 1994).

A final consideration regards the neural underpinnings of MV, TTD, and CON, indicated by the present study as modulating the instrumental-Pavlovian interaction. After a shock, the goal of avoiding punishment in the future (MV in our analysis) increased, leading to performance improvement. Goal values are encoded by orbitofrontal cortex and amygdala (Balleine and O'Doherty, 2009). In relation to threat distance, it is well known that emotional stimuli are partially processed by distinct neural structures compared to neutral stimuli (Vuilleumier and Driver, 2007). On the base of this, an intriguing possibility is that perceptual information on temporal and spatial threat distances preferentially activates amygdala, which is crucial for elaborating emotional stimuli. Moreover, perceptual information on threat distance might reach the amygdaloid nuclei through the direct thalamo-amygdala pathway, which has been hypothesized to be recruited by highly salient emotional stimuli (Vuilleumier and Driver, 2007). Finally, in relation to CON, evidence indicates that serotoninergic dorsal raphé nuclei and ventromedial prefrontal cortex implement CON at the neural level (Amat et al., 2005; Maier and Watkins, 2005). In particular, dorsal raphé nuclei would lead to uncontrollability effects, whereas ventromedial prefrontal cortex, by inhibiting the former structure, would oppose to those effects.

CONCLUSION

The study of the interaction between different motivational controllers is fundamental for understanding decision-making. On this basis, we investigated the Pavlovian-instrumental interaction, particularly underexplored in humans. Similarly to animal studies, the present findings support the view that Pavlovian responses impact on instrumental performance in humans too, and can produce misbehavior. In addition, amount of experience, shock expectancy, threat distance, punishment history, and task difficulty modulated the effect of Pavlovian responses on performance.

The Pavlovian-instrumental interaction could underlie some forms of irrationality in decision-making. Indeed, although Pavlovian mechanisms are possibly adaptive in most situations, nonetheless, in irrational decision-making, they might influence behavior in a way that is not congruent with the subject's goals. However, it does not necessarily follow that, in these cases, Pavlovian mechanisms are irrational or non-optimal in absolute terms. Rather, Pavlovian and instrumental controllers might just follow different optimality criteria. In particular, instrumental controllers would follow optimality in ontogenetic terms, in the sense that they might be guided by reward maximization on the base of the organism's experience. On the contrary, Pavlovian controllers would follow optimality in phylogenetic terms, in the sense that they might be guided by reward maximization on the base of the specie's experience (Dayan et al., 2006). Research on this topic could help elucidating important phenomena, apparently irrational, in economics, social behavior, and psychopathology (Dayan and Seymour, 2008).

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APPENDIX

THE TRIAL-BY-TRIAL MODEL-BASED ANALYSIS

We compared different trial-by-trial models of data, including different combinations of the ANOVA factors plus CON and MV. In order to operationalize MV and CON, we adopted a temporal-difference algorithm. This algorithm is a standard way for modeling variables depending on the history of motivational experience, like MV and CON. Indeed, MV (corresponding to the learned motivational values) depends on the history of past shocks, whereas CON (corresponding to the learned belief of performing well) depends on the history of success.

We considered the two Stimuli (CS+ and CS−) as distinct conditions for the computation of MV. Similarly, we considered the two Velocities (Fast and Slow) as distinct conditions for the computation of CON. Specifically, the MV associated to each trial depended on the MV associated to the previous trial of the same Stimulus condition, updated according to the shock-related outcome obtained in that previous trial. The following temporal-difference algorithm was used as learning rule (Sutton and Barto, 1998):

$$\mathrm{MV}_{\mathrm{STIM}n+1} = \mathrm{MV}_{\mathrm{STIM}n} + \mathrm{LR} \cdot (R - \mathrm{MV}_{\mathrm{STIM}n})$$

Where R represented the shock outcome of the trial ($R = 0$ if shock was avoided; $R = -1$ if shock was collected), LR represented the learning rate (LR), and the starting MV value was set to zero. It is important to note that, according to this learning mechanism, MV = 0 in CS− condition. In relation to CON, we operationalized it as a number comprised between 1 (when the participant has the maximum control on the environment) and zero (when the participant has not control at all). The CON associated to each trial depended on the CON associated to the previous trial belonging to the same Velocity condition, updated according to the outcome obtained in that previous trial. The following temporal-difference algorithm was used as learning rule (Sutton and Barto, 1998):

$$\mathrm{CON}_{\mathrm{VEL}n+1} = \mathrm{CON}_{\mathrm{VEL}n} + \mathrm{LR} \cdot (B - \mathrm{CON}_{\mathrm{VEL}n})$$

Where B represented the outcome of the trial ($B = 1$ if the trial was won; $B = 0$ if the trial was lost), LR represented the learning rate, and the starting CON value was set to 0.5. We used this starting value because, in absence of any clue on the participants' prior CON, it assigns the same probability (0.5) to the two possible outcomes (winning and losing).

We delimited the analysis to Blocks 1 and 2. To represent the trial-by-trial dynamics, we used logistic regression, which is based on a linear equation used to compute the probability of an outcome of a dichotomous variable, in our case the probability of winning at a given trial:

$$P(B = 1) = \frac{1}{1 + e^{(-\mathrm{MODEL})}}$$

Model parameters were inferred using the Least Square Method. The goodness of each model was estimated through the Akaike information criterion (AIC) index, and the parameters were assumed to be random variables across subjects, and were tested using independent-samples T-tests. The different models are shown in **Table 2**. Model 5 corresponds to the ANOVA model used for the analysis of the aggregated data, and was used as baseline model:

$$\mathrm{MODEL}\,5 = \alpha + \beta \cdot \mathrm{BLOCK} + \gamma \cdot \mathrm{VEL} + \delta \cdot \mathrm{STIM} + \varepsilon \cdot \mathrm{VEL} \cdot \mathrm{STIM}$$

In a pool of further models, we included also either MV or CON (multiplied by STIM in this latter case), as operationalized above. In addition, we tested different LRs (0.1; 0.4; 0.7; 1) for updating MV and CON in the models implementing these variables.

On the basis of the AIC index, no models implementing CON were better than the ANOVA model. On the contrary, some models implementing MV had a lower AIC compared to the ANOVA model. Overall, the model implementing the ANOVA model plus MV with a LR = 0.1 (model 9) resulted the best one (AIC = 6576). This result was corroborated also by the log-likelihood ratio test comparing the ANOVA model and model 9, made upon the mean negative log-likelihood across subjects [$\chi(1) = 12$; $p = 0.000$]. Finally, T-tests indicated that all model 9 parameters were statistically significant [two-tailed independent-samples T-tests: $\beta: T(37) = 2.58$, $p = 0.01$; $\gamma: T(37) = -4.48$, $p = 0.000$; $\delta: T(37) = 3.72$, $p = 0.000$; $\varepsilon: T(37) = -4.76$, $p = 0.000$; $\zeta: T(37) = -6.14$, $p = 0.000$]. Importantly, the MV parameter was negative, indicating that performance increased with the increasing of the number of past shocks.

As a final step of the trial-by-trial analysis, we assessed the effect of a shock or an error collected in the previous trial, by including in the model the shock-related outcome and/or the outcome collected in the previous trial (model 38, 39, and 40). AIC indexes indicated that all these models performed worse than model 9.

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Complexity and competition in appetitive and aversive neural circuits

Crista L. Barberini[1], Sara E. Morrison[2], Alex Saez[1], Brian Lau[3] and C. Daniel Salzman[1,4,5,6,7]*

[1] Department of Neuroscience, Columbia University, New York, NY, USA
[2] Department of Psychiatry and Behavioral Science, Albert Einstein College of Medicine, Bronx, NY, USA
[3] Centre de Recherche de l'Institut du Cerveau et de la Moelle Épinière, Paris, France
[4] Department of Psychiatry, Columbia University, New York, NY, USA
[5] Kavli Institute for Brain Sciences, Columbia University, New York, NY, USA
[6] W. M. Keck Center on Brain Plasticity and Cognition, Columbia University, New York, NY, USA
[7] New York State Psychiatric Institute, New York, NY, USA

Edited by:
Philippe N. Tobler, University of Zurich, Switzerland

Reviewed by:
Kae Nakamura, Kansai Medical University, Japan
Anton Ilango, National Institutes of Health, USA

***Correspondence:**
C. Daniel Salzman, Department of Neuroscience, Columbia University, 1051 Riverside Drive, Unit 87, New York, NY 10032, USA.
e-mail: cds2005@columbia.edu

Decision-making often involves using sensory cues to predict possible rewarding or punishing reinforcement outcomes before selecting a course of action. Recent work has revealed complexity in how the brain learns to predict rewards and punishments. Analysis of neural signaling during and after learning in the amygdala and orbitofrontal cortex, two brain areas that process appetitive and aversive stimuli, reveals a dynamic relationship between appetitive and aversive circuits. Specifically, the relationship between signaling in appetitive and aversive circuits in these areas shifts as a function of learning. Furthermore, although appetitive and aversive circuits may often drive opposite behaviors – approaching or avoiding reinforcement depending upon its valence – these circuits can also drive similar behaviors, such as enhanced arousal or attention; these processes also may influence choice behavior. These data highlight the formidable challenges ahead in dissecting how appetitive and aversive neural circuits interact to produce a complex and nuanced range of behaviors.

Keywords: amygdala, orbitofrontal cortex, value processing, reward, punishment

THE IMPORTANCE OF LEARNING TO PREDICT REINFORCEMENT FOR PUNISHMENT-BASED DECISION-MAKING

The decision-making process – arguably one of the most important "executive" functions of the brain – can be influenced by a variety of different types of information and motivators. Punishment-based decisions constitute an important subcategory that is common to a wide phylogenetic range, from nematodes to rodents to humans. Studies old and new have shown that punishment engages brain systems specialized for processing aversive information (Seymour et al., 2007). Historically, these systems have been studied most frequently in rodents, and this work has revealed many aspects of the neural mechanisms driving behavior elicited by the threat of aversive stimuli (Davis, 1992; LeDoux, 2000). In everyday life, however, decisions typically require integrating information about potential punishments *and* rewards, as well as myriad factors such as external environment and internal drives. This is especially true in primates, as they exhibit particularly complex behavioral repertoires.

Rewards and punishments are reinforcers with opposite valence (positive versus negative), and they often drive behavior in opposite directions – e.g., approaching a rewarding stimulus or avoiding a threat. Moreover, punishment-based decisions are often made in a context in which rewards and punishments are both possible consequences of an action; therefore, brain systems processing aversive information must interact with brain systems processing rewards – interactions that presumably underlie how punishments and rewards compete to drive behavior and decision-making. Scientists have long appreciated these facts and have often posited that appetitive and aversive systems operate in an "opponent" manner (Konorski, 1967; Solomon and Corbit, 1974; Dickinson and Dearing, 1979; Grossberg, 1984; Daw et al., 2002). However, appetitive and aversive stimuli also have certain common attributes – e.g., they are both usually more salient than non-reinforcing stimuli – and thus appetitive and aversive systems need not always act in opposition to each other. Rather, stimuli of both valences may mediate a number of processes, such as enhanced arousal or enhanced attention to stimuli predictive of reinforcement (Armony and Dolan, 2002; Anderson, 2005; Lang and Davis, 2006; Phelps et al., 2006; Brosch et al., 2008; Ilango et al., 2010; Pinkham et al., 2010; Anderson et al., 2011).

Punishment-based decisions are generally choices that are based on one or more prior experiences with an aversive outcome. Typically, an organism learns that a sensory cue predicts a possible negative outcome – e.g., the taste of spoiled food precedes illness – and later must decide what to do to avoid or defend against that outcome. Thus, learning to anticipate negative outcomes is an essential skill for subsequently being able to make optimal decisions in the face of possible punishment. This is also true for rewards: the adaptive response is to acquire the reward, rather than avoid it, but anticipation is critical in both cases.

Because accurately predicting reinforcement – whether punishment or reward – plays such a vital role in decision-making, our work has focused on understanding the neurophysiological processes whereby the brain comes to predict reinforcement as a result of learning. We have sought to understand where and how

signals in the brain represent anticipated positive or negative outcomes, and whether those signals occur at a time and in a manner such that they could be used as input to decision-making processes. We have often referred to these signals as *value* signals. Although our published studies have not characterized these signals during an explicit decision-making task, the tasks we employed do provide measures that appear to co-vary with the amount and type of the reinforcement associated with a stimulus (Paton et al., 2006; Belova et al., 2007, 2008; Salzman et al., 2007; Morrison and Salzman, 2009, 2011; Morrison et al., 2011). We believe that the *value* of anticipated possible outcomes often drives behavior, and the estimation of value may be computed on-line during decision-making by taking into account expected potential reinforcement as well as a variety of internal variables (e.g., hunger or thirst) and external variables (e.g., how difficult a reward would be to acquire; Padoa-Schioppa, 2011). We refer to the circuits that process and generate appetitive and aversive reinforcement predictions as value processing circuits, although in some cases work remains to be done to understand how different internal and external variables impact representations of reinforcement predictions.

Where in the brain does processing about reinforcement predictions occur? Early work indicated that the amygdala, a key structure in the limbic system, plays a central role in processing one of the primary negative emotions, the fear elicited by a stimulus predicting aversive consequences. Seminal fear conditioning studies in rats found that both learning and memory of fearful events required an intact, functional amygdala (Davis, 1992; LeDoux, 2000; Maren and Quirk, 2004). Since then, it has become clear that the purview of the amygdala extends beyond fear to include other emotions, including positive ones (Holland and Gallagher, 1999; Baxter and Murray, 2002; Everitt et al., 2003; Paton et al., 2006; Belova et al., 2008; Morrison and Salzman, 2010; Salzman and Fusi, 2010). These results suggest that the amygdala may carry signals related to the computation of both positive and negative value.

How do amygdala signals come to impact behavior? The amygdala is heavily interconnected with many other areas of the brain, providing an array of anatomical pathways by which it can participate in learning and decision-making. It receives input from multiple sensory modalities (McDonald, 1998; Amaral et al., 2003; Freese and Amaral, 2005), which accords with the amygdala's established role in associative learning; information from predictive sensory cues converges with input about reinforcing outcomes at the single cell level (e.g., Romanski et al., 1993). Furthermore, lesions of the amygdala impair reinforcer devaluation (Baxter and Murray, 2002; Izquierdo and Murray, 2007), indicating that the amygdala plays a role not only in learning reinforcement contingencies, but also in adjusting these representations as the value of associated reinforcement outcomes changes.

Although the amygdala participates in learning stimulus-reinforcement associations that in turn may be utilized and adjusted during decision-making, it does not act alone in these processes. The amygdala has reciprocal connections with orbitofrontal cortex (OFC; McDonald, 1991; Carmichael and Price, 1995; Stefanacci and Amaral, 2000, 2002; Ghashghaei et al., 2007), a cortical area thought to play a central role in value-based decisions (Padoa-Schioppa and Assad, 2006; Wallis, 2007; Padoa-Schioppa, 2011). OFC may be important for implementing executive or cognitive control over behavior, and endowing subjects with the ability to rationally analyze their options, as well as to tune their behavior to what is socially acceptable in the face of emotionally driven impulses (Damasio, 1994; Rolls, 1996; Bechara et al., 2000; Berlin et al., 2005; Ochsner and Gross, 2005). Part of this may be due to the fact that OFC seems to play a role in the simple ability to anticipate aversive stimuli or negative outcomes, as well as positive outcomes (Tremblay and Schultz, 2000; Roberts et al., 2004; Young et al., 2010).

In this paper, we review our efforts to understand the roles of the amygdala and OFC in acquiring representations of reinforcement contingencies. As we reviewed above, these representations may be critical substrates for reward-based and punishment-based decision-making. One of the striking findings in these investigations concerns the differential dynamics of processing that takes place in appetitive and aversive systems in amygdala and OFC. The amygdala appears to have evolved an aversive system that learns changes in reinforcement contingencies more rapidly than its counterpart in OFC; but, for appetitive networks, the time courses of learning in the two brain areas are reversed. Moreover, both single unit and local field potential (LFP) data point to complex interactions between amygdala and OFC that change as a function of learning. Although appetitive and aversive systems have been posited to act in an opponent manner, this complex pattern of interactions suggests that a more nuanced framework may be required to understand the relative contribution of these networks during learning and decision-making. Moreover, behavioral evidence indicates that appetitive and aversive stimuli can have a variety of effects on cognitive processes, some of which may be induced by stimuli of either valence. Altogether, these data suggest that appetitive and aversive systems may act in congruent *and* opponent fashions – even at the same time – and do not merely compete to determine the most valuable behavioral option during decision-making.

POSITIVE AND NEGATIVE CELLS IN THE BRAIN

We have focused on trying to understand neural circuits involved in punishment and aversive learning, and how these circuits may differ from and interact with circuits involved in rewards and appetitive learning. When we began our experiments several years ago, only a few studies had examined the neurophysiology of the amygdala in primates (Sanghera et al., 1979; Nishijo et al., 1988, 2008; Rolls, 2000; Sugase-Miyamoto and Richmond, 2005; Wilson and Rolls, 2005). Furthermore, no primate lab had undertaken simultaneous recordings in amygdala and OFC to understand dynamic interactions between the brain structures during learning.

Our experimental approach strove to disambiguate neural responses that might be related to the sensory properties of visual conditioned stimuli (CSs) from responses related to the reinforcement contingencies. To accomplish this, we used a mixed appetitive/aversive reversal learning paradigm. This paradigm combined a conditioning procedure with standard extracellular physiology in rhesus monkeys; we measured the physiological responses of individual neurons to CSs that signaled an impending positive or negative US. CSs were small fractal patterns, positive outcomes

were small aliquots of water, and negative outcomes were brief airpuffs directed at the face (Paton et al., 2006; Belova et al., 2007, 2008; Morrison and Salzman, 2009, 2011; Morrison et al., 2011). In these experiments, one CS was initially paired with reward and another with an aversive stimulus (unconditioned stimuli, USs); then, without warning, we reversed the reinforcement contingences of the CSs. We recorded single neuron responses while monkeys learned the initial CS-US associations and their reversal. One major advantage of this approach was that reinforcements – particularly aversive "punishments" – were unavoidable, so we were able to unequivocally identify neural activity related to the anticipation of appetitive and aversive reinforcement.

In both the amygdala and OFC, we observed two populations of neurons that fired more for positive or negative outcomes, respectively, which we refer to as positive and negative value-coding cells. The response profiles for these two populations are shown in **Figures 1A–D** for OFC and in **Figures 1E–H** for the amygdala. Shortly after CS onset, both cell populations systematically fire differentially for CSs paired with positive or negative reinforcement. Reversing the reinforcement contingencies (**Figures 1C,D,G,H** for positive and negative cells, respectively) demonstrates that the differential firing is specifically related to the reinforcement contingencies and not other aspects of the CS, such as specific visual features. Note that after reversal, an image formerly associated with a reward now leads to a punishment, and vice-versa; after only a few trials of exposure to these new contingencies (Paton et al., 2006; Belova et al., 2007; Morrison et al., 2011), the neural response pattern shifts to reflect these changes, such that the response profiles look quite similar before and after reversal.

The encoding of reinforcement contingencies seems to reflect the overall motivational significance, or *value*, of a US associated with a CS, and not other types of information learned during conditioning. Several lines of evidence support this conclusion. First, neither amygdala nor OFC neurons encode motor responses elicited by USs on our task, indicating that neurons do not appear to represent the relationship between a CS and the motor response elicited by USs (Paton et al., 2006; Morrison and Salzman, 2009). Second, both OFC and amygdala neurons generally do not simply represent the relationship between a CS and the sensory qualities of a preferred US. Rather, we found that OFC and amygdala neurons respond in a graded manner to CSs predicting large rewards (LRs), small rewards (SRs), and negative outcomes; this means that a cell that prefers a CS associated with an aversive airpuff also responds differentially to CSs associated with water rewards, and thus encodes information about two types of outcomes. Moreover, since the outcomes include two modalities (taste and touch), it is unlikely that the neural response is primarily driven by a physical quality of one type of outcome, such as the strength or duration of the airpuff (Belova et al., 2008; Morrison and Salzman, 2009).

Third, positive and negative neurons often appear to track value in a consistent manner across the different sensory events in a trial – including the fixation point, CS, and US presentations – even though those stimuli differ in sensory modality. This has led us to suggest that amygdala and OFC neurons represent the overall value of the animals' "state," or situation (Belova et al., 2008; Morrison and Salzman, 2009, 2011). Finally, in an additional series of experiments that examined the representation of "relative" value

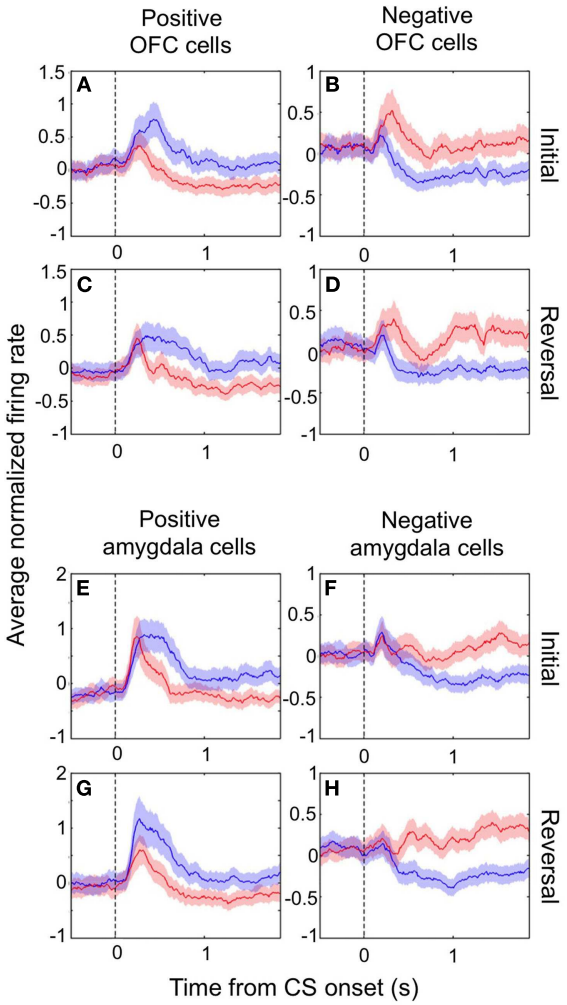

FIGURE 1 | Value-coding cells in the amygdala and OFC. The average normalized neural activity (±SEM) as a function of time since CS onset is shown for the population of positive value-coding cells **(A,C,E,G)** and negative value-coding cells **(B,D,F,H)**, in OFC **(A–D)** and the amygdala **(E–H)**. Responses are shown before **(A,B,E,F)** and after **(C,D,G,H)** reversal of the outcome contingencies associated with each CS. Peristimulus time histograms (PSTHs) were built using 10 ms non-overlapping bins, *Z*-scoring, and then averaging cells together, and lastly smoothing by calculating a 10-bin moving average. Blue lines, positive CS trials; red lines, negative CS trials. Vertical dotted line, CS onset. Adapted from Morrison et al. (2011), Figure 3, with permission.

in different contexts, amygdala neurons changed their firing rate in accordance with changes in the relative value of a CS, even when the absolute value (i.e., reward size) of the associated US does not change (Schoer et al., 2011). This phenomenon has also been observed in the OFC (Padoa-Schioppa, 2009; Schoer et al., 2009).

In contrast to the signals just described, there are doubtless other signals in the brain that encode the magnitude of single stimulus dimensions – e.g., the size or taste of specific rewards. However, these signals would not, in and of themselves, be sufficient to inform choices made between outcomes that were in different modalities.

DYNAMICS DURING LEARNING

The neurons we describe provide a dynamic representation that changes rapidly during learning. Overall, during reversal learning, the change in the neural responses in both amygdala and OFC was on a timescale similar to changes in the monkey's behavior. Behavioral metrics of the monkey's expectation – anticipatory licking of the water tube preceding rewards and anticipatory "blinking" before aversive airpuffs – reversed within a few trials, indicating that monkeys learned the new associations quite rapidly (Paton et al., 2006; Morrison et al., 2011). Amygdala and OFC neural activity likewise began to change their responses to CSs within a few trials of a reversal in reinforcement contingencies (Paton et al., 2006; Belova et al., 2007; Morrison et al., 2011). This sequence of neural and behavioral changes indicates that the amygdala and OFC could be involved in the monkeys' learning of new reinforcement contingencies.

Neuroscientists have long believed that the prefrontal cortex, and OFC in particular, drives reversal learning (Iversen and Mishkin, 1970; Thorpe et al., 1983; O'Doherty et al., 2001; Schoenbaum et al., 2002; Chudasama and Robbins, 2003; Fellows and Farah, 2003; Hornak et al., 2004; Izquierdo et al., 2004; Chamberlain et al., 2008; Hampshire et al., 2008; Ghahremani et al., 2010); but some have recently proposed that in fact representations in OFC may update more slowly upon reversal than those elsewhere (Schoenbaum et al., 1998, 2003; Saddoris et al., 2005). Because we recorded amygdala and OFC activity simultaneously, we were able to examine the dynamics of learning in positive and negative value-coding neurons in both amygdala and OFC in order to characterize their relative timing. We found that appetitive and aversive networks in OFC and amygdala exhibited different learning rates, and – surprisingly – that the direction of the difference depended on the valence preference of the cell populations in question. For positive cells, changes in OFC neural activity after reversal were largely complete many trials earlier than in the amygdala; for negative cells, the opposite was true (**Figure 2**). In each case, the faster-changing area was completing its transition around the time of the onset of changes in behavior; meanwhile the other, more slowly changing area did not complete the shift in firing pattern until many trials after the behavioral responses began to change. Thus, signals appropriate for driving behavioral learning are present in both brain structures, with the putative aversive system in the amygdala and appetitive system in OFC being particularly sensitive to changes in reinforcement contingencies. This finding may reflect the preservation across evolution of an aversive system in the amygdala that learns very quickly in order to avoid threats to life and limb.

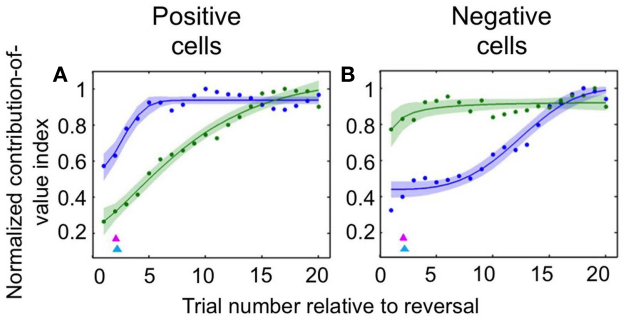

FIGURE 2 | Comparison of the time courses of learning-related activity in positive and negative value-coding neurons in the amygdala and OFC. Normalized average contribution of image value to neural activity, derived from ANOVA, plotted as a function of trial number after reversal for positive value-coding neurons **(A)** and negative value-coding neurons **(B)**. Blue lines, OFC; green lines, amygdala; red and cyan arrowheads, mean licking and blinking change points, respectively. Adapted from Morrison et al. (2011), Figures 5C,D, with permission.

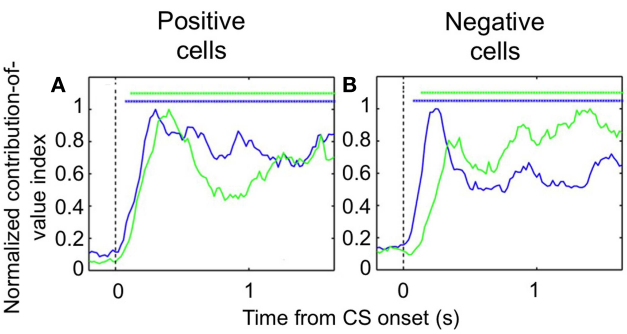

FIGURE 3 | Encoding of image value in OFC and the amygdala. The contribution of image value as a function of time for positive value-coding cells **(A)** and negative value-coding cells **(B)**. Asterisks, time points at which the average contribution of value is significant (Fisher $p < 0.0001$) for OFC (blue lines) and the amygdala (green lines). Vertical dotted line, CS onset. Adapted from Morrison et al. (2011), Figures 8E,F, with permission.

DURING VERSUS AFTER LEARNING

Despite the complex pattern of dynamics we observed during learning, once the new CS-US contingencies have been established, we found that *both* populations of OFC cells – positive value-coding and negative value-coding – predict reinforcement earlier in the trial than their counterparts in the amygdala (**Figure 3**). To demonstrate this, we examined trials after learning had taken place and determined the earliest point in the trial each area begins to significantly differentiate between images that predict reward and images that predict airpuff. For both positive and negative cell populations, OFC predicted reinforcement more rapidly after image onset. Thus, it appears that the relationship between single unit firing in the appetitive and aversive networks in the two brain areas evolves as a function of learning, with the OFC perhaps assuming a more primary role after learning.

We found further evidence of the evolving dynamic relationship between amygdala and OFC during learning by examining LFP data recorded during the reversal learning task. To do so, we applied Granger causality analysis, which measures the degree to which the past values of one neural signal predict the current values of another (Granger, 1969; Brovelli et al., 2004), to the simultaneously recorded LFPs in the amygdala and OFC. Remarkably, we found significant Granger causality in *both* directions that increased upon CS onset (Wilcoxon, $p < 0.01$; **Figure 4A**). Notably, during learning, Granger causality was stronger in the amygdala-to-OFC direction, but after learning, Granger causality

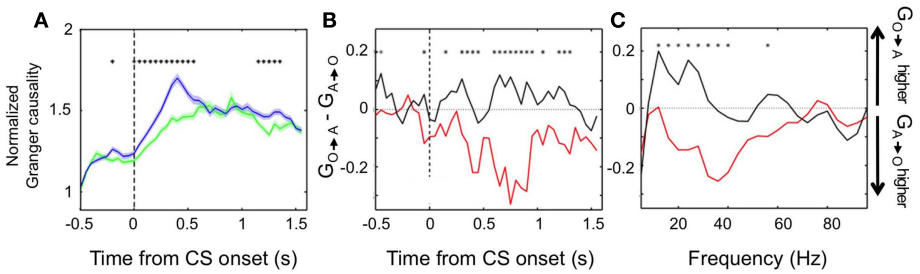

FIGURE 4 | Granger causality between the amygdala and OFC. (A) Average normalized Granger causality (±SEM) for the OFC-to-amygdala direction (blue) and the amygdala-to-OFC direction (green). For each pair of OFC-amygdala LFP recordings, Granger causality was computed for all trials after reversal, then averaged across pairs. Only pairs with significant Granger causality at some point during the trial were included in the average, which combines frequencies from 5 to 100 Hz. Asterisks, bins with significantly different causality for the two directions (permutation test, $p < 0.05$). **(B,C)** Granger causality changes with learning. The difference between the mean Granger causality in the two directions (subtracting amygdala-to-OFC from OFC-to-amygdala) was separately calculated for early (during learning, red line) and late (post-learning, black line) trials after reversal. This comparison is shown for all frequencies 5–100 Hz as a function of time within the trial **(B)** and for the CS and trace intervals combined as a function of frequency **(C)**. Asterisks, bins where the difference between during-learning and post-learning values was significant (permutation test, $p < 0.05$). Adapted from Morrison et al. (2011), Figure 9, with permission.

was strongest in the OFC-to-amygdala direction (**Figures 4B,C**). This result is consistent with single unit data showing that, after reversal learning has occurred, OFC predicts reinforcement with a shorter latency after CS onset. This positions the OFC to be able to drive or modulate amygdala responses to value-laden CSs after learning. (Note, however, that the amygdala continues to be able to influence processing in OFC, just not as strongly as the reverse.).

CONFLICT WITHIN APPETITIVE AND AVERSIVE CIRCUITS

There is an additional level of complexity within appetitive and aversive circuits that has not received much attention on the physiological level, namely competition and conflict within these circuits. Our learning data suggest that the signals carried by different neural circuits may be updated at different rates in different brain areas. This suggests that these systems might at times conflict with each other. Another possible example of competition is that between executive areas – which allow us to evaluate potential outcomes on a practical and rational level – and limbic areas, which are more involved in emotional processing, and which might provide a value signal based more heavily on immediate sensory experience and emotion-laden associations. For example, the amygdala and OFC themselves may at times "recommend" different responses, the former mediating more emotionally driven responses and the latter more executive or cognitive behaviors (De Martino et al., 2006).

This phenomenon has been given some attention on the behavioral level (McNeil et al., 1982; Damasio et al., 1994; Kahneman and Tversky, 2000; Loewenstein et al., 2001; Greene and Haidt, 2002), and has also been examined using fMRI in humans (McClure et al., 2004, 2007; De Martino et al., 2006; Kable and Glimcher, 2007). However, few studies have examined appetitive and aversive circuits at the level of single cells during a decision-making task involving rewards and punishments. To best investigate the interactions between appetitive and aversive neural circuits, such a decision-making task should include conditions in which rewards and aversive stimuli must be weighed against each other in order to guide behavior. As a first step, we trained monkeys to perform a simple two-choice task involving rewards and aversive stimuli (described below). We discovered that, even on this simple task, behavioral choices appear to be influenced not only by the value of the reinforcement associated with cues, but also by the salience of cues.

We used a two-choice task in which monkeys selected visual targets by making a saccade to the target of their choice. Monkeys viewed two visual targets on each trial, each of which was a CS associated with a particular outcome. After maintaining fixation during a 900–1200 ms delay period, monkeys chose one of the two targets by foveating it, followed by delivery of the associated outcome (**Figure 5A**). There were four possible outcomes: a LR, a SR, no reinforcement (N), or a punishment (P), where rewards were small amounts of water and punishments were brief airpuffs directed at the face. The four CSs (one for each outcome; **Figure 5B**) were offered in all possible combinations, with the exception of two of the same kind. Trial conditions were pseudo-randomly interleaved, and counter-balanced for spatial configuration. The list of trial types is shown in **Figure 5C**. New sets of CSs were used in each session. Two independent stimulus sets were used, and trials drawing from the two sets were interleaved in pseudo-random order. In each session, a pair of locations on the monitor was chosen and used for the duration of the session. The locations varied, but each pair always straddled the fixation point. While monkeys were free to choose either target, they had to make a choice: incomplete trials were repeated until one or the other target was chosen.

If monkeys always chose the higher-value target, then plotting the percent of trials on which a CS was chosen, out of all trials on which that CS was offered, yields a straight line, since LR is always the higher-value target when presented, SR on 2/3 of trials when presented, N on 1/3 of trials, and P on no trials, as can be seen in the list of trial conditions (see **Figure 5C**). We will refer to this as "optimal" behavior. In **Figure 6**, two example sessions are shown. The first is a session in which a monkey chose the higher-value target most of the time, such that the plot of the number of times each target was chosen follows the optimal behavior line quite closely

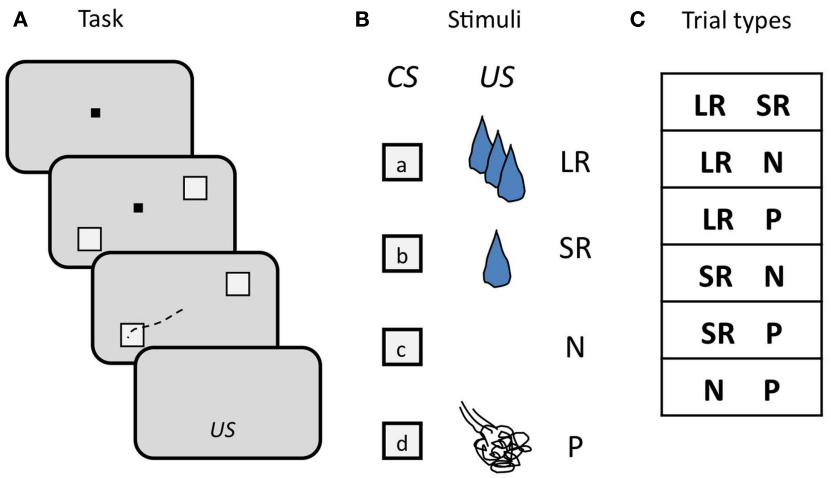

FIGURE 5 | Schematic illustration of the design of the two-choice task. **(A)** Sequence of events in each trial. The monkey begins each trial by foveating a central fixation point (FP, black square), then two visual targets appear, straddling the FP, a delay ensues, the FP goes out, and the monkey makes an eye movement (black dashed line) to one of the two targets to select it. Targets are extinguished, and, after another short delay, the associated outcome (US) is delivered. **(B)** Visual targets (CSs) and associated outcomes (USs). Four targets are used as CSs, each one associated with one of the four possible USs. CSs are random grayscale stick figures (not shown); USs: LR, large reward; SR, small reward; N, neutral; P, punishment. **(C)** Trial types, determined by the outcome of the two CSs offered. CSs were counter-balanced for location.

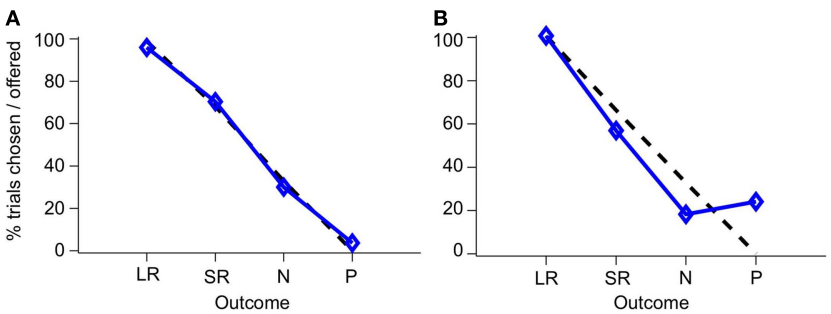

FIGURE 6 | Choice behavior in the two-choice task. The percent of trials that a CS was chosen when it was offered is shown for each CS. Blue line, monkey's choices; dashed black line, optimal behavior. Choice behavior is shown for two sessions, one where the monkey rarely chose the P target **(A)**, and one where he chose it frequently **(B)**. The two stimulus sets have been combined in this figure.

(**Figure 6A**). In the second example, however, the same monkey chose the punished target many times, and about as often as he chose the neutral (non-reinforced) target (**Figure 6B**).

The deviation from optimal behavior seen in **Figure 6B** is not due to an overall drop in performance, but to a change in behavior on a single trial type: the N-P stimulus pair. In **Figure 7**, a running local average of the proportion of trials on which the monkey chose the higher-value target is shown, broken down by trial type, for the same two sessions shown in **Figure 6**. When offered a choice between a reward and a punishment, the monkey reliably chose the reward (LR-P and SR-P trial types in **Figures 7A,B**). However, when offered a choice between no reinforcement and a punishment, in some sessions, the monkey chose punishment quite often (N-P trial type in **Figure 7B**). These two sessions are representative of the type of choice behavior we observed.

This choice pattern was perplexing to us at first. We noticed that sometimes monkeys avoided the punished target in a session, while other times he chose it over the neutral target a substantial fraction of the time. We checked and manipulated a number of parameters: did monkeys find the punishment aversive? Was it aversive *enough*? Did monkeys understand the CS-US contingencies? What we found, in two monkeys, was an abundance of evidence that subjects *did* understand the task contingencies, *did* find the airpuff aversive, and yet chose the punished target despite the aversive outcome they knew would follow. Evidence in support of the idea that the airpuff was indeed aversive included: visible frustration and displeasure upon airpuff delivery, defensive blinking behavior in anticipation of airpuff, statistically significant greater likelihood of breaking fixation on N-P trials, and willingness to work being clearly dependent on the strength or frequency of airpuff delivery, with increases in any of these variables quickly

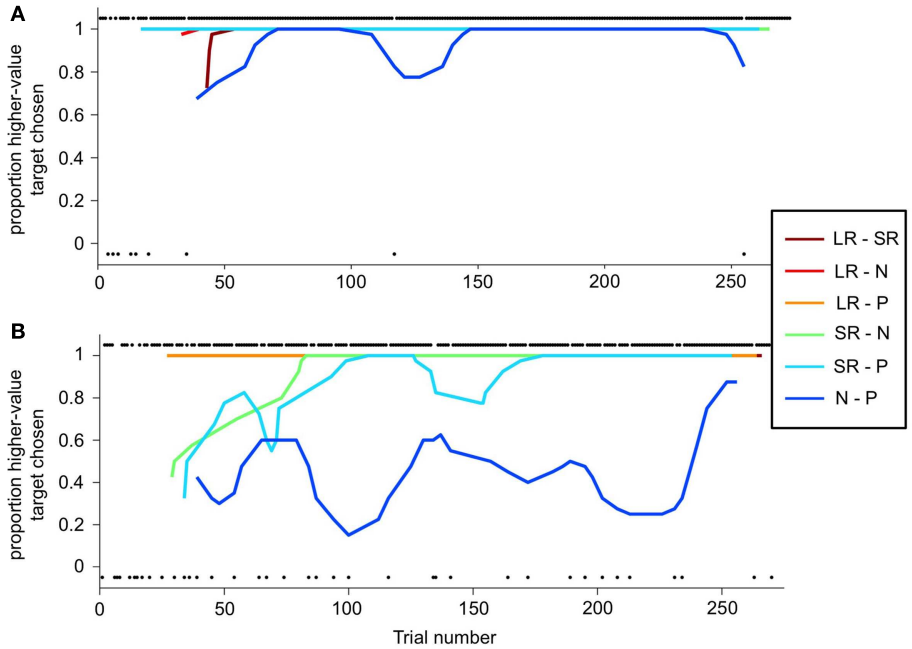

FIGURE 7 | Choice behavior as a function of trial number. (A,B) A running average is calculated (6-trial boxcar) for each trial type (the two stimulus sets are again folded together), as a function of trial number within the session, for the same sessions shown in **Figure 6**. Choice behavior on each trial is calculated as the proportion of higher-value targets chosen, and on each trial is either 1 (higher-value target was chosen) or 0 (lower-value target was chosen). Individual black dots show when one outcome or the other was chosen on a per-trial basis. Thus, dots along the bottom of the figure indicate a lower-value choices. Dots are offset from 0 to 1 for clarity. Running average lines start at different trial numbers because they start on the *n*th trial for that trial type, where *n* is the width of the running average, but are plotted against actual trial number in the session.

leading to the monkey's refusing to work for the rest of the day. None of these were observed in relation to rewarding outcomes.

Over a period of training lasting several months, these patterns persisted. **Figure 8** shows the performance across a series of sessions over a period of a few weeks in one monkey. The two example sessions shown in the previous figures are marked with asterisks. In **Figure 8A**, the percent of trials completed for N-P versus other trial types is displayed. On average, the monkey broke fixation before completing the trial more often on N-P trials than on other trial types – resulting in a lower percent of trials completed – which is indicative of that trial type being aversive, difficult, or both. (Note that the two sessions shown in **Figures 6** and **7** are not representative of this overall pattern, having lower than average percent break-fixation trials). **Figure 8B** shows the percent of trials on which the monkey chose the N-target on N-P trials (dark gray bars, %N of NP) as compared to choosing the P target (light gray bars). What is apparent is that %N of NP varied day to day, and did not appear to plateau at a stable level, nor was there a trend in either direction as training progressed. Note that the selection of the punished target on N-P trials occurred during blocks in which, on all other interleaved trial types, the monkey chose the higher-value target nearly all of the time (**Figure 8C**). This same pattern was seen in other training periods for this monkey, as well as across all training periods in the second monkey.

On average, one monkey chose neutral CSs over punished CSs only slightly more than half the time. **Figure 9A** shows the distribution of %N of NP across all training sessions, including the subset shown in **Figure 8**. The mean was 62.2%, and was significantly greater than 50% (t-test, $p < 0.0001$). This was over a training period of 5 months, and after trying a host of manipulations to ensure that the monkey understood the task and the CS-US contingencies involved. Also, note that on interleaved trials, the monkey was choosing the higher-value target virtually all the time (**Figure 9B**). In the second monkey, the average %N of NP was very close to 50%, and was not statistically significant (mean, 50.4%, mean > 50%, t-test, $p = 0.4409$), even though that monkey was also trained extensively and exposed to the same set of task manipulations as the first monkey. However, his performance on other trial types was similarly very high (mean, 89.1% higher-value target chosen, mean > 50%, t-test, $p < 0.0001$).

While there are several possible explanations of this counter-intuitive behavior, we favor one explanation that fits with some of the other examples of neural systems in competition. In particular, we believe that on the N-P trial type, the salience and value of cues were in conflict, and this conflict pushed monkeys toward different choices. This was not true on any of the other trial types, in which the most salient CS on the screen was also the most valuable (whatever the highest level of reward was). On N-P trials, however, the N-target is more valuable than the P target (presumed zero value versus negative value), but the P target, by virtue of its association with an aversive airpuff, is very likely to be more salient. Thus the P target is chosen some of the time, even though it is not necessarily what monkeys prefer, due to a strong impulse to foveate – i.e., look at or orient toward – this

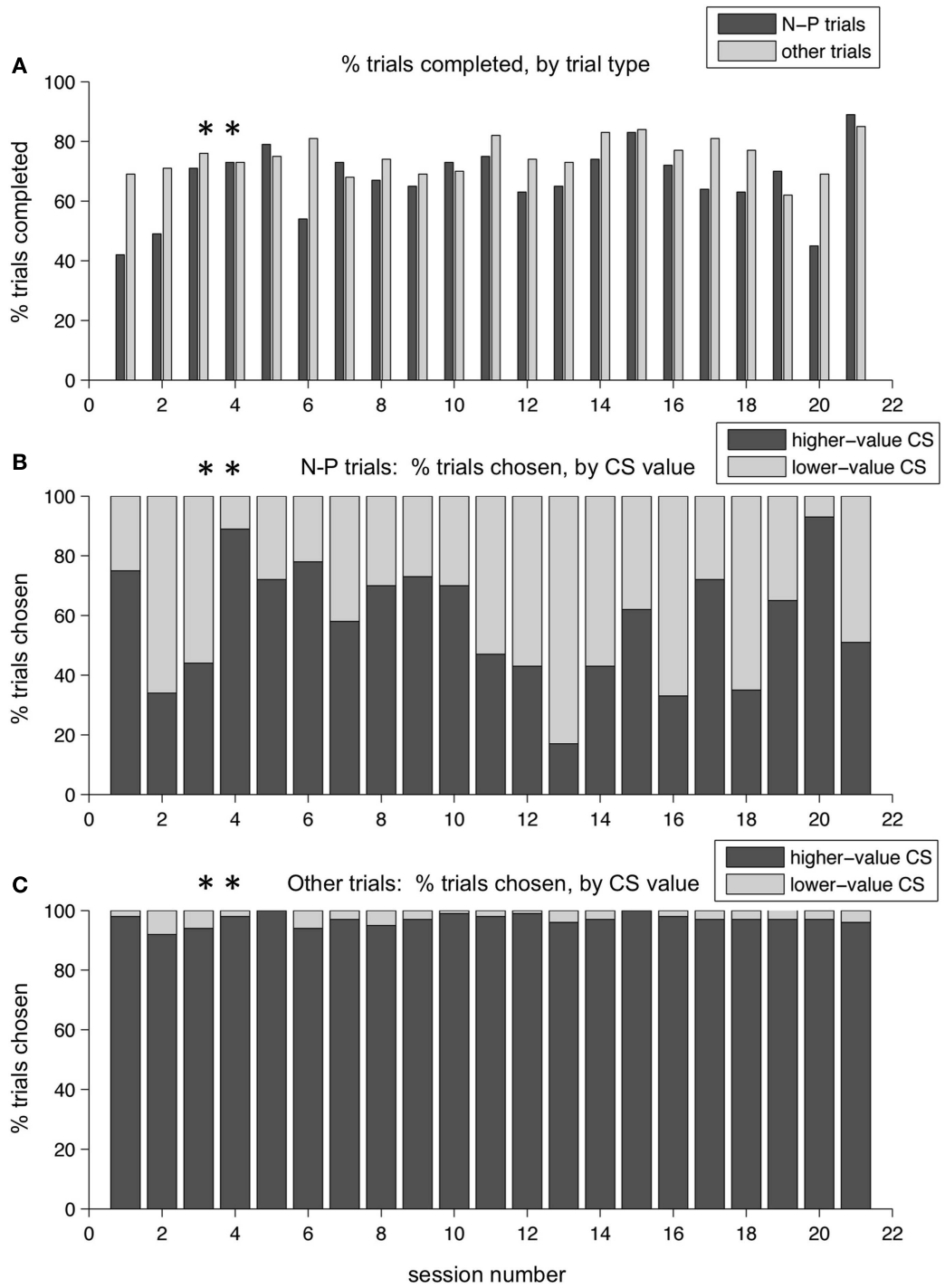

FIGURE 8 | Choice behavior in the two-choice task over time. Performance over a training period of weeks for one monkey. **(A)** The percent of trials completed is shown, for each session, for N-P trials and all other trials separately (dark and light gray bars, respectively). **(B)** The percent of N-P trials, for each session, on which the monkey chose N (higher-value CS, dark gray bars) or P (lower-value CS, light gray bars). **(C)** The percent of other trial types, for each session, on which the monkey chose the higher-value target (dark gray bars) or the lower-value target (light gray bars). Asterisks mark the two sessions shown in **Figures 6** and **7**.

highly salient, behaviorally relevant stimulus. Further evidence to support this idea is that monkeys were much more indecisive on N-P trials than on other trials: this was apparent in the percentage of break-fixation trials (**Figure 8A**), and in the observation that monkeys often looked quickly back and forth between targets, even though this behavior led to a greater number of incomplete

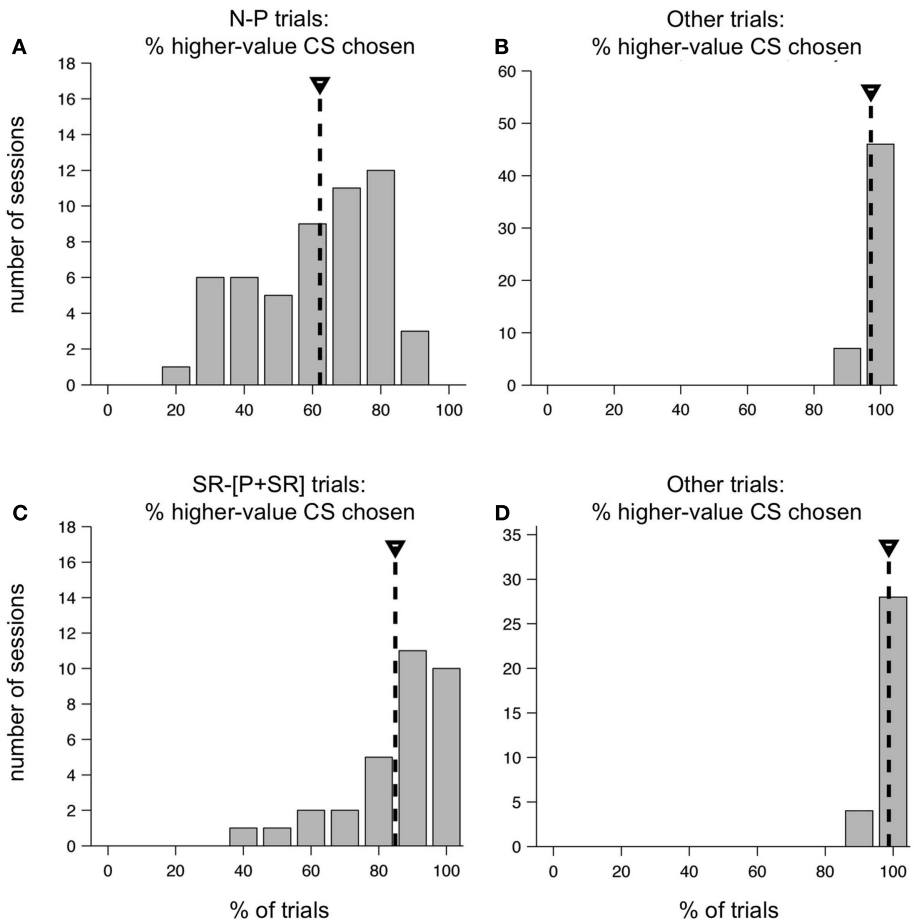

FIGURE 9 | Distribution of higher-value target choices in two versions of the two-choice task. Performance of one monkey in the original two-choice task **(A,B)** and the modified two-choice task **(C,D)**. **(A)** Distribution of the percent of N-target choices on N-P trials across all sessions in a 5 month training period. Mean, 62.2% (mean > 50%, *t*-test, $p < 0.0001$). **(B)** Distribution of the percent higher-value choices on non-N-P trial types across the same set of sessions as in **(A)**. Mean, 97.1% (mean > 50%, *t*-test, $p < 0.0001$). **(C)** Distribution of the percent of SR-target choices on SR−[P + SR] trials across 32 sessions. Mean, 84.9%, (mean > 50%, *t*-test, $p < 0.0001$). **(D)** Distribution of the percent higher-value choices on non-SR−[P + SR] trial types across the same set of sessions as in **(C)**. Mean, 98.7%, (mean > 50%, *t*-test, $p < 0.0001$).

trials. The monkeys did not do this on other trial types. As might be expected for trial types that are more difficult or less certain, monkeys exhibited greater spatial bias on N-P trials than on other trial types. The differences were modest: first monkey, 10.0% versus 1.6% bias, and second monkey, 8.3% versus 2.4% bias, for N-P and other trials, respectively, when measured across all sessions. (Bias is the percentage over 50% that a preferred spatial location is chosen; a 10% bias is equivalent to a location being chosen 60% of the time). While both differences were statistically significant (*t*-test, $p < 0.0001$ in both cases), the small magnitude indicates that other factors had a strong impact on the monkeys' choices.

We suspected that the absence of a possible reward on N-P trials was having a major impact on the choice behavior of our monkeys. Therefore, we redesigned the task for the first monkey so that all outcomes included some level of reward, using as our set of possible outcomes: LR, SR, and a compound outcome of airpuff and SR (P + SR). For the compound outcome, the punishment was delivered first, followed by a short delay and then the SR. This change resulted in a substantial shift in the monkey's behavior. Within a few training sessions, the monkey learned the new task and began consistently choosing the higher-value target most of the time on all trial types. At the beginning of each session, new CSs were introduced, and the monkey learned them within a small number of repetitions, and then chose the higher-value target virtually all of the time for the rest of the session. The monkey performed at this level consistently day after day: the average choice %SR on the trial type SR−[P + SR] was 84.9% (**Figure 9C**), which was significantly greater than 50% (*t*-test, $p < 0.0001$), and variations around this mean were much smaller than they had been in the first version of the task. As before, on all other trial types, which were interleaved, the monkey chose the higher-value target virtually all of the time (**Figure 9D**).

We have here, then, an example of counter-intuitive choice behavior that is robust and occurs when no reward is possible. As we mention above, we suspect that this is due to competition between the neural circuits processing value and salience;

we would also speculate that the salience of negative outcomes only grows large enough to compete with value signals driving behavior when the value of the alternative outcome is small or zero (e.g., when a cue predicts no reinforcement). Clearly, this results in sub-optimal choice behavior. This is consistent with other studies that have noted sub-optimal performance in tasks where monkeys are forced to make a choice between outcomes and the greatest possible reward is very small or zero. For example, Peck et al. (2009) observed more incorrect choices on "neutral" as opposed to rewarded trials, and Amemori and Graybiel (2012) observed longer reaction times and more omission errors on a "reward–reward" control task when reward size was very low. Moreover, Amemori and Graybiel (2012) designed their main experimental task to include a SR for any choice because they found it necessary to "maintain motivation to perform the task." The paradigm employed by Amemori and Graybiel differed from ours in a number of ways, including the use of a joystick movement operant response, limiting our ability to make a direct comparison of the behavior observed in the two tasks. On the other hand, our use of an eye movement operant response may have increased the efficacy by which representations of salience modulated behavior. There is good reason to believe that salience has privileged access to the oculomotor system (Bisley et al., 2004; Hasegawa et al., 2004), especially in the highly visually oriented primate, to promote rapid foveation of salient stimuli.

We suggest that our behavioral results may be an example of a competition between limbic and cortical circuits dedicated to emotional versus cognitive processing, respectively. This paradigm, in the macaque, may test the limits of the amount of cognitive control monkeys are able to exert over reflexive behaviors. While the monkey does succeed in overriding the impulse to look at the punished target some of the time, he does not do so all of the time. Humans, with their greater level of cognitive processing and control, would presumably have much less difficulty avoiding the punished target.

SUMMARY AND CHALLENGES

To make a decision, we often must predict how particular stimuli or courses of action lead to rewards or punishments. The ability to make these predictions relies on our ability to learn through experience the relationship between stimuli and actions and positive and negative reinforcement. It is therefore important to understand the representation of aversive and appetitive outcomes in the brain, both during and after learning, in order to understand how these signals generate behavior. However, at the same time, it's important to recognize that the impact of appetitive and aversive circuits is not limited to behavior that is specific to the valence of the looming reinforcement. Activation of appetitive and aversive circuits can also elicit valence non-specific responses, such as enhanced arousal or attention.

A number of the studies in our lab have been directed at trying to understand the nature of appetitive and aversive circuits in the brain. Although there hadn't been a great deal of work examining aversive processing at the physiological level in non-human primates in the past, some older studies suggested that our approach would be fruitful (e.g. Nishijo et al., 1988; Mirenowicz and Schultz, 1996; Rolls, 2000; Yamada et al., 2004). Our neurophysiological studies have expanded on these initial findings to create a more detailed picture of appetitive and aversive circuits. Both the amygdala and OFC contain neurons that belong to each network: positive and negative value-coding neurons are present in both areas, and appear to encode the value of cues that signal imminent appetitive and aversive reinforcers, responding in a graded fashion to the value of CSs as well as USs. The dynamics of learning exhibited by appetitive and aversive networks in amygdala and OFC are surprisingly complex, with aversive systems updating faster during reversal learning in the amygdala than OFC, but vice-versa for appetitive networks (Morrison et al., 2011). This suggests that reversal learning is not merely driven by one brain area or the other. The complexity of the dynamics is also illustrated by the fact that the degree to which each area may influence the other is not fixed and instead evolves during the learning process (Morrison et al., 2011) and perhaps in other circumstances as well.

In addition to our neurophysiological findings, behavioral data indicates that the interactions between appetitive and aversive systems are complicated. In a paradigm that required monkeys to make decisions based on the value of stimuli, behavior was sub-optimal when monkeys had to choose between a cue associated with nothing and a cue associated with an airpuff. These results indicate that eye movement choice behavior may be influenced not just by the value of stimuli but also by their salience. It demonstrates that competition between appetitive and aversive networks may occur not only between the values encoded by the two systems but also by the extent to which the systems influence brain structures representing salience, and thereby perhaps generating enhanced attention and eye movements to salient targets.

The complexity of interactions between appetitive and aversive circuits is likely to remain an enduring problem for neuroscientists, but headway is being made. Notably, in our studies of the amygdala and OFC, we have failed to find evidence of anatomical segregation of appetitive and aversive networks (Morrison et al., 2011). Rather, appetitive and aversive networks appear to be anatomically intermingled. Anatomical segregation of these systems would make it easier to develop experimental approaches that can target manipulations of one system or the other to test their causal role in behavior. Fortunately, some recent studies have begun to identify areas where anatomical segregation exists. Two examples of segregation in aversive systems may be found in the work of Hikosaka and colleagues on the habenula (Matsumoto and Hikosaka, 2007, 2008, 2009), and Graybiel's team in the ACC (Amemori and Graybiel, 2012). The habenula appears to encode negatively valenced stimuli in relation to expectation. The ACC contains networks belonging to appetitive and aversive networks, though there appears to be some anatomical segregation of the aversive network. Both areas are likely to be involved in value-driven decision-making and/or learning. In addition, in contrast to our findings in the monkey, anatomical segregation of appetitive and aversive processing has been observed in the OFC in human fMRI studies (Kim et al., 2006). Our recordings focused only on a restricted part of OFC, largely area 13, and it remains possible that recordings from a more extensive part of the OFC will reveal anatomical segregation of appetitive and aversive systems in the macaque. In general, anatomical segregations may provide

more experimentally tractable opportunities for future studies to elucidate details concerning how each network operates.

Despite the anatomical segregation of some aspects of these networks, the challenges ahead are formidable. The amygdala and OFC are two structures intimately related to emotional processing, and these structures, among others, likely mediate the executive control of emotion. Moreover, the amygdala, through its extensive connections to sensory cortex, to the basal forebrain and to the prefrontal cortex is poised to influence cognitive processing. The neurophysiological data we have presented illustrates the complexity of interactions between appetitive and aversive networks. Further, the behavioral data presented suggests that conflict between appetitive and aversive networks extends beyond conflicts about value to conflicts between value and salience. Future studies must clarify how these conflicts are resolved in the brain.

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AUTHORIZATION FOR USE OF EXPERIMENTAL ANIMALS

All experimental procedures were in accordance with the National Institutes of Health guidelines and were approved by the Institutional Animal Care and Use Committees at New York State Psychiatric Institute and Columbia University.

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Organization of neural systems for aversive information processing: pain, error, and punishment

Shunsuke Kobayashi*

Department of Neurology, Fukushima Medical University, Fukushima, Japan

Edited by:
Philippe N. Tobler, University of Zurich, Switzerland

Reviewed by:
Jeansok J. Kim, University of Washington, USA
Veit Stuphorn, Johns Hopkins University, USA

****Correspondence:***
Shunsuke Kobayashi, Department of Neurology, Fukushima Medical University, 1 Hikarigaoka, Fukushima-shi, Fukushima-ken 9601295, Japan.
e-mail: skoba-tky@umin.net

The avoidance of aversive events is critically important for the survival of organisms. It has been proposed that the medial pain system, including the amygdala, periaqueductal gray (PAG), and anterior cingulate cortex (ACC), contains the neural circuitry that signals pain affect and negative value. This system appears to have multiple defense mechanisms, such as rapid stereotyped escape, aversive association learning, and cognitive adaptation. These defense mechanisms vary in speed and flexibility, reflecting different strategies of self-protection. Over the course of evolution, the medial pain system appears to have developed primitive, associative, and cognitive solutions for aversive avoidance. There may be a functional grading along the caudal-rostral axis, such that the amygdala-PAG system underlies automatic and autonomic responses, the amygdala-orbitofrontal system contributes to associative learning, and the ACC controls cognitive processes in cooperation with the lateral prefrontal cortex. A review of behavioral and physiological studies on the aversive system is presented, and a conceptual framework for understanding the neural organization of the aversive avoidance system is proposed.

Keywords: amygdala, periaqueductal gray, orbitofrontal cortex, anterior cingulate cortex, prefrontal cortex, error-related negativity, pain, reward

INTRODUCTION

The nervous system has multiple mechanisms for protecting organisms against harmful events. Reflexes in the spinal cord and brainstem provide the most primitive form of defense, such as withdrawing a hand upon touching a hot object. Association learning is a higher mechanism that allows organisms to anticipate harmful events. Since the aversive consequences may be damaging or even fatal, organisms cannot afford many exposures thereto, and aversive learning must be sufficiently fast. Harmful events may be avoided by cognitive functions such as performance monitoring, error detection, and top-down attention control.

This paper discusses the neural mechanisms underlying aversive avoidance, focusing on two aspects. First, it may be important to understand how the neural system implements aversive avoidance. Because it is so critical for survival, the avoidance system must have developed under great evolutionary pressure. There seem to be multiple avoidance mechanisms reflecting different evolutionary stages. Thus, understanding the neural organization of the aversive system may provide insight into its evolution and development. Second, the aversive system is an essential counterpart of the reward system. An important issue is thus how the brain processes the information of opposing valences. In theory, rewarding and aversive events can be encoded on one scale in the positive and negative ranges, respectively. Alternatively, events of the opposite valences may be processed by distinct neural networks. **Figure 1** illustrates the possible encoding of rewarding and aversive events, where the bars indicate hypothetical neural activities in response to appetitive, motivationally neutral, and aversive events. Preferential excitation or suppression of appetitive events with reference to neutral events indicates that neurons are sensitive to positive value (**Figures 1A,B**). Conversely, preferential excitation or suppression to aversive events indicates a negative value coding (**Figures 1C,D**). Single neurons may encode both positive and negative ranges on the value scale, such that high activity reflects positive (appetitive) value and low activity reflects negative (aversive) value (**Figure 1E**), or vice versa (**Figure 1F**). Another possibility is that neurons respond to both appetitive and aversive events in the same direction, but not to neutral events (**Figures 1G,H**). This type of response encodes motivational intensity, possibly reflecting the level of attention or arousal.

PERCEPTION OF AVERSIVE STIMULI

The perception of aversive stimuli is crucial for the survival of organisms. Noxious stimuli applied to the skin activate various brain areas including the thalamus, primary somatosensory cortex (S1), anterior insular cortex, periaqueductal gray (PAG), amygdala, and anterior cingulate cortex (ACC; Jones et al., 1991; Talbot et al., 1991; Coghill et al., 1994; Hutchison et al., 1999; Koyama et al., 2001; Iwata et al., 2005). Thus, nociceptive input is processed in distributed sensory networks. Previous studies have suggested the presence of a crude dichotomy of sensory processing, namely into the lateral cortical pathway for sensory localization and discrimination, and the medial subcortical-limbic pathway (or medial pain system) for processing affective and motivational significance based on sensory information (**Figure 2**; Vogt et al., 1993a; Schnitzler and Ploner, 2000; Vogt and Sikes, 2000; Zhang et al., 2011).

The medial pain system includes the medial and intralaminar thalamic nuclei, ACC, and projections from these areas to nociception-regulating centers such as the PAG (Vogt et al., 1993b).

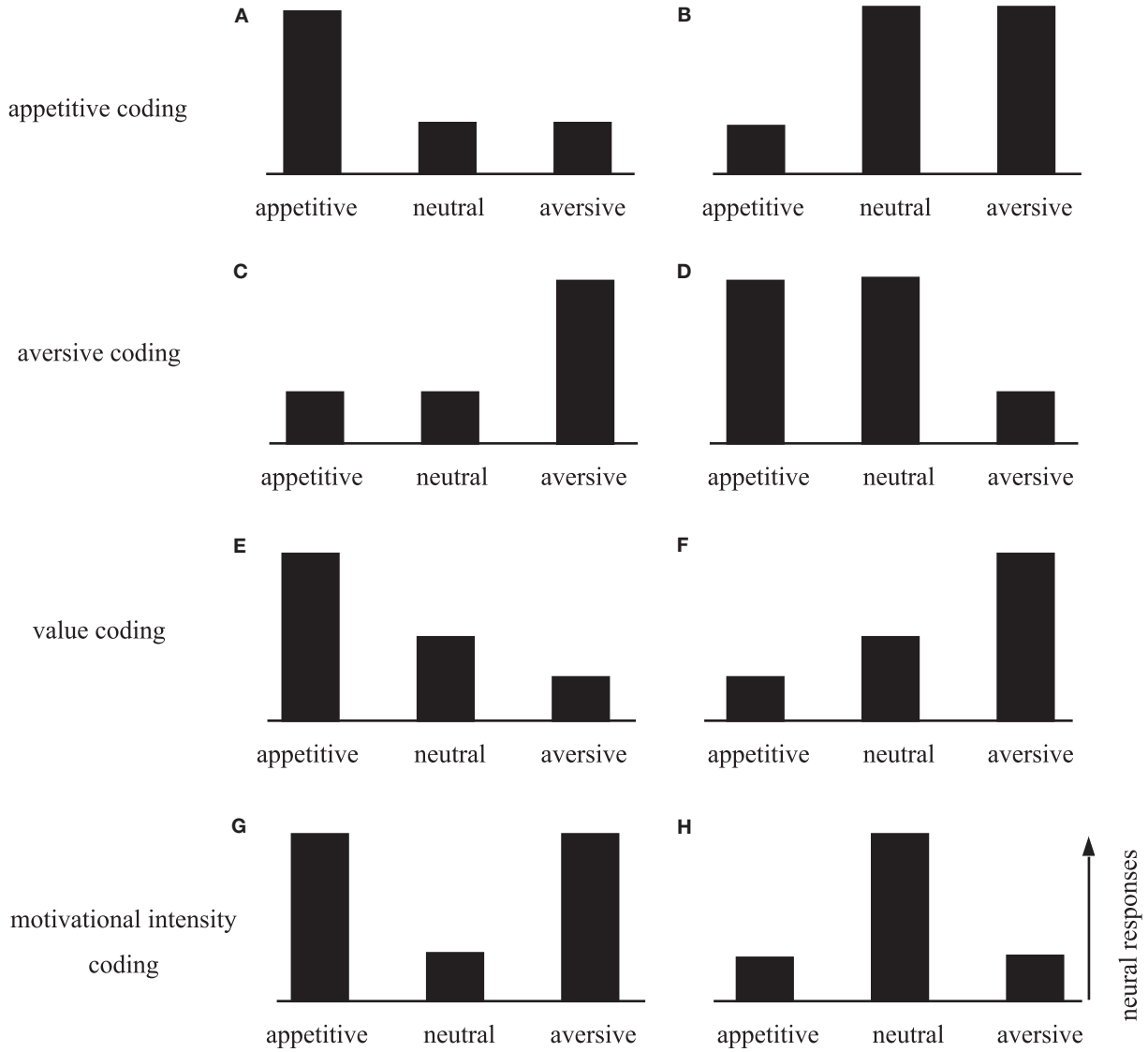

FIGURE 1 | Schematic diagram of the neural response patterns to appetitive, neutral, and aversive stimuli. Neurons that selectively process appetitive information would be selectively activated **(A)** or suppressed **(B)** by appetitive stimuli. In this case, the responses to aversive and neutral stimuli would not differ. Similarly, neurons in the aversive system would exhibit selective activation **(C)** or suppression **(D)** to aversive stimuli. Single neurons may encode both appetitive and aversive information on the value scale, such that high activity reflects a positive (appetitive) value and low activity reflects a negative (aversive) value **(E)**, or vice versa **(F)**. Neurons may encode motivational intensity independent of valence. Neural responses may be enhanced **(G)** or suppressed **(H)** by motivationally significant stimuli regardless of whether they are appetitive or aversive. These types of responses may be related to attention or arousal level.

The PAG receives inputs from the axon collaterals of spinothalamic projections and is connected reciprocally with the medial thalamic nuclei and the central nucleus of the amygdala. The PAG has been implicated as a key player in the descending noxious inhibitory system (Le Bars et al., 1979). The involvement of the PAG in pain control has been demonstrated by analgesic effects caused by opiate injection and electrical stimulation in the PAG (Mayer and Liebeskind, 1974; Bennett and Mayer, 1979; Yaksh et al., 1988).

The ACC is linked to the medial pain system via its medial thalamic afferents and projections to the PAG. The ACC is thought to receive nociceptive inputs from the medial and intralaminar thalamic nuclei (Hsu and Shyu, 1997). Nociceptive neurons in the ACC have characteristically extensive dendritic arbors in layer IIIc, where the thalamic projection terminates (Vogt et al., 1981). Complete disconnection of ACC from the S1 does not abolish nociceptive responses in the ACC, which indicates that nociceptive responses in the ACC are independent of those in the S1 (Sikes and Vogt, 1992). High-density opiate receptors in the ACC also support its role in pain perception. Neural populations in the ACC responds to dermal stimulation by noxious CO_2 laser with short- and long-latency components of possibly A-δ and C-fiber origins, respectively. Intraperitoneal administration of morphine

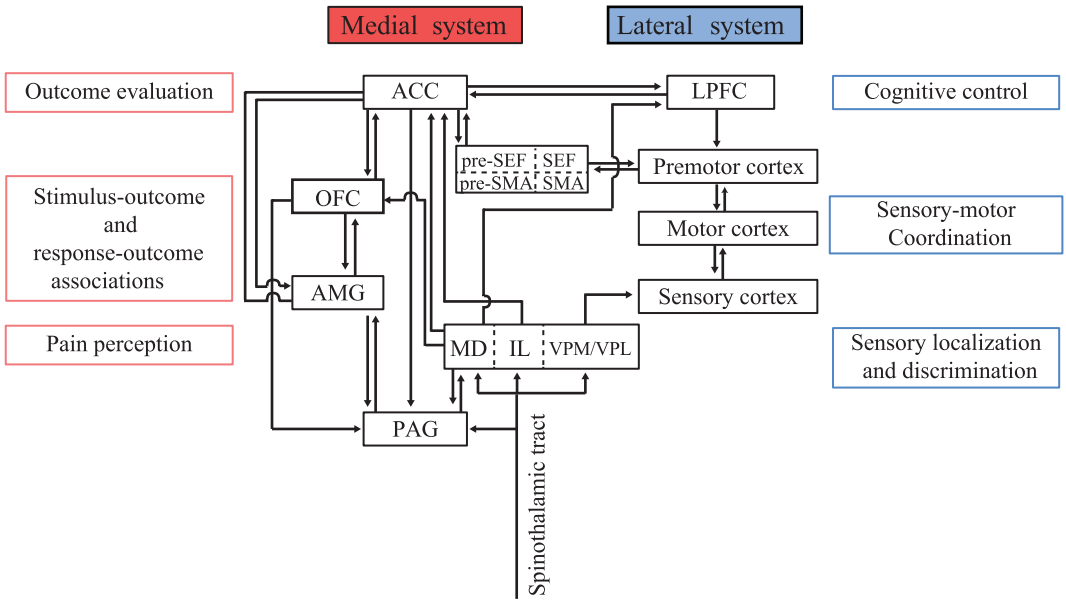

FIGURE 2 | Conceptual schema illustrating the functional dichotomy between the medial and lateral systems. The medial system includes the amygdala (AMG), periaqueductal gray (PAG), orbitofrontal cortex (OFC), and anterior cingulate cortex (ACC), and serves as a predictor and evaluator of behavioral outcomes. The lateral system receives multimodal sensory inputs and processes the signals to obtain physical information regarding the environment. Sensory information is transferred to the LPFC for cognitive decision-making and action planning. The ACC provides feedback information to the LPFC to implement behavioral adaptation based on outcome values. MD, mediodorsal nucleus of the thalamus; IL, intralaminar nucleus of the thalamus; VPM/VPL, ventral posteromedial nucleus/ventral posterolateral nucleus of the thalamus; SMA, supplementary motor area; pre-SMA, presupplementary motor area; LPFC, lateral prefrontal cortex.

significantly attenuates both of these components in the ACC (Kuo and Yen, 2005). It has been proposed that the phasic nociceptive responses in the ACC are mediated by the thalamus, and the long-duration responses may underlie integrative processes following the primary thalamic-mediated nociceptive responses (Shyu et al., 2010). It is also known that cingulate lesions reduce affective responses to noxious stimuli without disrupting sensory localization (Foltz and White, 1962; Ballantine et al., 1967).

A study on rabbits examined the neuronal responses to visceral pain caused by balloon distension applied to the colon and cutaneous pain caused by thermal and electrical stimuli applied to the skin (Sikes et al., 2008). A group of ACC neurons exhibited a viscerocutaneous response (39.1%), while others were exclusively visceral (37.3%) or exclusively cutaneous (22.6%). That study also found that the nociceptive response was not strictly limited to the ACC, with pain being more extensively represented in the medial frontal area including midcingulate and retrosplenial cortices.

The medial pain system may also be involved in the motor and autonomic responses induced by aversive stimuli. For example, the freezing response to electric shock is thought to be elicited via the amygdala-PAG pathway in rats (Ledoux et al., 1988; Amorapanth et al., 2000) and cats (Hopkins and Holstege, 1978; Amorapanth et al., 2000), although its course downstream from the PAG remains unclear. The medial raphe nucleus is also involved in freezing and other anxiety-related responses, such as increased micturition, defecation, crouching, and piloerection (Graeff and Silveira Filho, 1978). Lesioning the medial raphe nucleus suppressed fear-induced behaviors but relatively preserved simple appetitive behaviors.

It is debatable whether the medial pain system responds preferentially to aversive stimuli or commonly to both rewarding and aversive stimuli. Few studies have examined the ACC responses to both appetitive and aversive stimuli. A primate single-unit study of the amygdala demonstrated the coexistence of both valence-sensitive and valence-insensitive neurons; some amygdala neurons exhibited differential responses to rewards only, others to punishments only, and some neurons to both rewards and punishments (Belova et al., 2007). Responses to appetitive and aversive stimuli appear to change according to context in both the amygdala and ACC. For example, the response to juice appears to differ markedly according to whether juice delivery is predicted (Koyama et al., 2001; Belova et al., 2007). Therefore, the sensory response of the ACC may not simply reflect sensory input *per se*, instead also being influenced by top-down modulation.

Harmful events may be perceived not only through somatosensory inputs but also through other sensory modalities, including odor and gustatory sensations. A question arises as to whether the neural system generates a generic aversive signal that does not depend upon a specific input modality. Neuroimaging studies have investigated the brain structures that are commonly activated by different modalities of aversive stimuli (e.g., aversive pictures and uncomfortable temperatures). Common aversive responses were found in the amygdala, anterior insular cortex, orbitofrontal cortex (OFC), and ACC (Hayes and Northoff, 2011). Together, these

findings suggest that the medial pain system signals the generic negative affects induced by multiple sensory modalities.

NEURAL CORRELATES OF AVERSIVE ASSOCIATION LEARNING

For wild animals, the presence of a predator's odor or footprints indicates impending danger and learning aversive associations is critically important for their survival. In the laboratory, rodents exhibit excitatory or inhibitory responses (i.e., startle, escape, and freezing) to an innocuous stimulus (i.e., a tone) that predicts a noxious stimulus (i.e., electric shock), and amygdala lesions cause behavioral impairments in these aversive conditioning (Pellegrino, 1968; Slotnick, 1973; Wilensky et al., 1999; Davis et al., 2003; Blair et al., 2005). Primate studies have also demonstrated behavioral impairments after amygdala lesions related to aversive avoidance, such as consuming unpleasant foods or the avoidance of predators or unfriendly conspecifics (Machado and Bachevalier, 2006; Machado et al., 2010).

Despite overwhelming evidence for the role of the amygdala in fear conditioning, neural signaling of aversive learning remains largely unclear. As for appetitive learning, reward prediction error theory has been proposed as a mechanism underlying the actions of the dopamine system, which enables associations between conditioned stimuli (CS) and appetitive unconditioned stimuli (US). According to that theory, behavioral adaptation is guided by a teaching signal that reflects the gap between predicted and actual reward outcomes. Most dopamine neurons reflect the reward prediction error; while animals learn the associations between CS (e.g., a picture) and US (e.g., juice), the initially present dopamine activations to appetitive US disappear and responses to CS emerge (Ljungberg et al., 1992; Schultz et al., 1997). Few studies have examined whether the prediction error theory applies to neural activities during aversive conditioning. Dopamine response during aversive learning may be a mirror image of that during reward learning, such that initial suppressions to aversive US disappear and suppressions to aversive CS emerge (Mirenowicz and Schultz, 1996; Matsumoto and Hikosaka, 2009; Cohen et al., 2012). Johansen et al. (2010) examined the influences of prediction on neural responses in the amygdala and PAG during fear conditioning. Unpredicted shock-evoked responses in both the amygdala and PAG, but these responses diminished when shock was predicted by CS. Furthermore, pharmacological inactivation of the PAG attenuated the shock-evoked responses in the amygdala and impaired acquisition of fear conditioning. Another study found that CS responses in amygdala neurons emerged during fear conditioning (Quirk et al., 1995). These results suggest that prediction error theory applies to the process of aversive learning in the dopamine system, amygdala, and PAG.

Another issue is whether the amygdala specializes in aversive conditioning in a valence-selective manner. Recent studies have suggested that the amygdala is involved in the behavioral responses to both appetitive and aversive reinforcements. Paton et al. (2006) recorded from amygdala neurons while abstract images acquired positive and negative values during conditioning with a liquid reward and air-puff, respectively. They found that distinct populations of amygdala neurons encode the positive and negative values of visual stimuli and that changes in neuronal activity correlated with the behavioral responses of anticipatory licking and eye blinking. It has also been found that some amygdala neurons are activated by both rewarding and aversive stimuli in the same direction, which may reflect the level of arousal or attention (Belova et al., 2007). Thus, although classically viewed as a center of fear, the amygdala seems to represent opponent motivational valences as well as motivational intensity.

It has also been suggested that the OFC is involved in association learning and value representation. Gottfried et al. (2002) used functional MRI (fMRI) in humans to study hemodynamic responses during odor-face conditioning, where initially neutral faces were repetitively paired with pleasant, neutral, or unpleasant odors. That study identified several key areas involved in olfactory associative learning, including the OFC, the nucleus accumbens, and the amygdala. Within the OFC, regions related to olfactory association learning were found rostral to the regions that show odor-evoked activity. Those authors demonstrated that olfactory input transforms from sensory to associative signals through caudal-to-rostral processing in the OFC. Other imaging studies have suggested the occurrence of compartmentalization of the opposing value signals within the OFC, with lateral activation in response to rewarding stimuli and medial activation in response to punishing stimuli (O'Doherty et al., 2001; Small et al., 2001).

Considering the extensive bidirectional anatomical connections, the amygdala and OFC are likely to have close functional interactions (Carmichael and Price, 1995; Morrison et al., 2011). With multimodal sensory afferents and the projections to the autonomic centers, the amygdala-OFC system is located strategically to underlie behavioral adaptation based on conditioning.

NEURAL BASIS OF ERROR DETECTION AND BEHAVIORAL ADAPTATION

Inappropriate behavior may lead to aversive outcomes. Such behavior may be suppressed through a process called operant conditioning, in which the associations between behavioral acts and their consequences are learned. Nevertheless, response errors may occur even after operant learning has progressed, such as in the presence of distraction, interference, or conflict. Empirical data show that subjects often recognize error commission and prepare for compensatory or defensive responses to upcoming aversive outcomes. One question is how error commission can be recognized before the associated negative outcomes are revealed.

Error-related negative (ERN) deflection of the EEG is probably the most replicated evidence for on-line neural processing of the occurrence of errors (Falkenstein et al., 1990). The ERNs have a symmetrical frontocentral distribution, and dipole modeling has consistently indicated that they originate from the medial frontal cortex, specifically in the ACC (Dehaene et al., 1994; Holroyd et al., 1998; Gehring et al., 2000). ERNs are elicited by incorrect responses in various tasks with different response modalities (e.g., hands, feet, and eyes; Holroyd et al., 1998; Nieuwenhuis et al., 2001). Miltner et al. (2003) required participants to press a button when they estimated that 1s had elapsed following presentation of a warning stimulus. At the end of the trial, a feedback stimulus indicated whether or not their estimate on that trial was within a criterion range. That study demonstrated that ERNs are elicited by error feedback, which was temporally dissociated with the occurrences

of behavioral response. Other studies replicated this finding by presenting error feedback in the auditory, visual, and somatosensory modalities. Thus, the ERNs appear to reflect neural error processing that is flexible and generic in that it is triggered by either motor responses or error feedback and that it depends on the modality of neither the behavioral response nor the sensory feedback.

Experiencing error feedback is not uncommon in our daily lives (e.g., a cash dispenser giving a beep sound when invalid PIN is typed). Error feedback serves as a negative reinforcer because we adapt our behavior to avoid receiving such signals. Feedback signals that are contingent upon error responses are usually human inventions (e.g., beep sound, flashing LED). Thus, learning based on error feedback might be considered to be unique to humans. However, animals also show behavioral adaptation based on negative feedback during operant tasks in laboratories. In theory, the violation of a response-outcome contingency is associated with prediction error, which serves as a teaching signal to guide reinforcement learning. It has been suggested by some researchers that dopamine neurons are a potential origin of ERNs, because they are known to carry prediction error signals and project to the medial frontal cortex (Holroyd and Coles, 2002). Alternatively, the medial frontal cortex may supply prediction error signals via its connections to the midbrain dopamine area. The association with the dopamine system suggests that ERNs should be driven by unexpected positive (successes and rewards) and negative (errors and punishments) events in opposing directions (**Figures 1E,F**). This hypothesis is supported by empirical data, and in particular for negative prediction errors. Holroyd and Coles (2002) found that a larger ERN was elicited by unexpected unfavorable outcomes than by expected unfavorable outcomes, which indicates that ERNs are correlated more strongly with negative prediction errors than with the negative outcomes themselves. Other studies have suggested that event-related potentials of medial frontal origin respond particularly strongly to outcomes that are considered aversive or signaling reductions in reward (Bush et al., 2002; Holroyd and Coles, 2002; Nieuwenhuis et al., 2004).

Primate studies also support the idea that the medial frontal cortex is involved in error-related processing. In a series of studies (Schall et al., 2002) used a saccadic stop-signal task, in which saccades that were supposed to reach peripheral targets had to be canceled upon presentation of a stop-signal. Surface EEGs recorded in monkeys exhibited a greater negative deflection when saccades were not canceled on stop trials than when saccades were correctly executed on no-stop trials (Godlove et al., 2011). This monkey homolog of ERNs is distributed in medial frontal areas, similar to human ERNs. It has also been shown that local field potentials (LFPs) and single-unit activities in the monkey ACC and supplementary eye field (SEF) are modulated on error commission (Niki and Watanabe, 1979; Stuphorn et al., 2000; Ito et al., 2003; Emeric et al., 2008, 2010). ACC neurons that show post-error activations were also found to be active when the expected reward was omitted after correct behavior responses (Niki and Watanabe, 1979). Thus, ACC neurons may not be simply "error-related," but may be reflecting negative reward prediction errors. On the other hand, LFPs in SEF were different from those in ACC in that they correlated with response conflict rather than reward prediction error (Emeric et al., 2008, 2010), suggesting that, unlike ACC, SEF is involved in sensory-motor processing.

In summary, there is growing evidence that ACC reflects prediction error in response-outcome contingencies. ERNs may be correlated more strongly with negative than with positive prediction errors (Chase et al., 2011), indicating predominantly aversive processing in the ACC (**Figures 1C,D**). Prediction error signals in the ACC may influence motor planning processes in the adjacent motor-related areas, including the SEF and supplementary motor area. Whether ERNs depend on dopamine input remains unclear; further investigation is needed in this field.

COGNITIVE CONTROL THEORY AND THE ACC

While the prediction error hypothesis of ERNs implies value-based learning, value-independent theories have also been proposed as underlying mechanisms. Perhaps the most popular is the cognitive control theory, according to which ERNs reflect top-down attention control exerted with high cognitive demand, such as when there is an interfering stimulus to be ignored or a prepotent response to be inhibited. A typical situation is found in the Stroop task, in which subjects are required to name the print colors of color words (Stroop, 1935). When a word name and its print color are incongruent, the prepotent word-reading response must be inhibited and the print color has to be named. This conflict increases the rate of response errors and the reaction time. Human neuroimaging studies have consistently shown ACC activation on conflict trials during Stroop and other conflict tasks, including the Eriksen flanker (Gratton et al., 1992; Botvinick et al., 1999) and Simon tasks(Sturmer et al., 2002). However, primate neurophysiological studies have failed to find a conflict signal during tasks that should engender response conflict (Nakamura et al., 2005; Emeric et al., 2008). Future investigation should clarify whether the observed physiological differences in conflict paradigms are due to technical issues (e.g., differences in behavioral tasks and recording methods), or due to species heterogeneity of the ACC functions and cognitive flexibility (Cole et al., 2009). Different perspectives on the role of ACC (conflict theory versus outcome-based decision-making) might be reconciled by a modified theory of conflict monitoring (Botvinick, 2007).

It is known that prior context influences the size of the behavioral interference effects on subsequent trials during conflict tasks. An example is an increase in the behavioral reaction time following an error. Such post-error slowing indicates a reactive adjustment in cognitive control that shifts the speed-accuracy trade-off for more accurate responding (Rabbitt, 1966). Another type of sequential effects is a faster reaction time after conflict trials: the conflict effect decreases when the previous trial was incongruent compared to when the previous trial was congruent (Sturmer et al., 2002; Wuhr and Ansorge, 2005). This post-conflict behavioral adjustment is interpreted to be a result of top-down control recruited additionally by conflict on the previous trial. Consistent with this idea, fMRI studies have shown that conflict-related activity in the ACC is reduced after conflict trials (Botvinick et al., 1999; Kerns et al., 2004). Also, the post-conflict behavioral adjustment is attenuated in patients with medial frontal injuries (Di Pellegrino et al., 2007). Womelsdorf et al. (2010) found that LFPs recorded in the ACC while monkeys responded to a peripheral stimulus according

to two stimulus-response (SR) mapping rules were selective for the SR mappings and stronger when behavioral adjustment was required following errors. These results suggest that the medial prefrontal cortex, and specifically the ACC, is involved in cognitive control based on conflict monitoring and error detection.

VALUE-BASED AND VALUE-INDEPENDENT MODELS FOR BEHAVIORAL ADJUSTMENT

Both reinforcement learning and cognitive control may guide decision-making and behavioral adaptation. However, they operate with different strategies and it has long been debated which strategy is implemented in the ACC and reflected in ERNs (Di Pellegrino et al., 2007). Reinforcement learning is a value-based algorithm, which would adjust behavioral output based on outcome evaluation. The dopamine and basal ganglia systems appear to operate under reinforcement learning algorithms. Thus, one possible hypothesis is that the medial pain system computes negative values based on reinforcement learning algorithms in parallel with reward computation in the dopamine and basal ganglia systems. In contrast, cognitive control theory is not directly concerned with outcome value. According to this theory, the ACC monitors cognitive demand and adjusts for allocation of cognitive resources. These two theories are not necessarily mutually exclusive: the mechanisms of reinforcement learning and cognitive control may coexist or cooperate in the ACC (Botvinick, 2007). Notably, the ACC is thought to be subdivided into areas of affects and cognition (Vogt, 1993; Devinsky et al., 1995). The affective division encompasses areas 25, 24, and 33, which have extensive connections with the amygdala and PAG. The cognitive division includes caudal areas 24′, 32′, and the cingulate motor areas, and the nociceptive cortex. Thus, heterogeneous functions may occur in different parts of the ACC.

INFLUENCE OF OUTCOME VALUE ON COGNITIVE PROCESSING

Environmental information is received as sensory input and its various physical features are processed in the cortical sensory areas. On the other hand, ventromedial brain structures, including the dopamine system, amygdala, OFC, and ACC, appear to play a key role in mapping sensory-motor information onto the scale of value (**Figure 2**). Given this functional dichotomy, how are decisions and action planning affected by the associated reward and punishment? There must be an interaction between the dorsolateral cognitive pathway and the ventromedial value pathway. Indeed, the influence of reward expectation on neuronal activities in various cortical areas has been found in many studies (Platt and Glimcher, 1999; Coe et al., 2002; Kobayashi et al., 2002). However, the influence of aversive outcomes has not been studied extensively.

We examined the influences of outcome value on the function of spatial working memory by recording single-unit activities in the lateral prefrontal cortex (LPFC; Kobayashi et al., 2006). Monkeys were required to remember the location of a briefly presented visual cue to perform a saccade response after a short delay. Correct responses were followed by liquid reward, air-puff avoidance, or neutral sound feedback. We found that a sizeable fraction of prefrontal neurons distinguished between rewarding and aversive outcomes. Most valence-discriminating neurons were sensitive to rewards (**Figure 3A**; cf. **Figures 1A,B**), although a small number of neurons showed activity that was preferentially modulated on aversive trials (**Figure 3B**; cf. **Figures 1C,D**). The results indicate that appetitive and aversive outcomes have independent influences on separate populations of LPFC neurons. Interestingly, a group of LPFC neurons exhibited modulation by both positive and negative reinforcers in the same direction (**Figure 3C**; cf. **Figures 1E,F**). Together, the LPFC appears to be equipped with both valence-specific and valence-non-specific reinforcement mechanisms, which would collectively contribute to outcome-based behavioral adaptation.

Another primate study examined the influence of reinforcement feedback on the LPFC and ACC (Rothe et al., 2011). LFPs were recorded while monkeys performed a problem-solving task. A correct target had to be searched by trial and error and then the correct responses could be repeated (repetition period). Error feedback caused high gamma power increases in the ACC, followed by a later increase in the LPFC during the search period. Correlations of high gamma activity were present during both the search and repetition periods, but correlations of beta power were predominant during the repetition period. Thus, feedback information appears to transfer from the ACC to the LPFC, and the functional coordination may use different LFP power bands depending on the task requirements. Evaluative signals in the ACC appear to trigger increased control by the LPFC.

There are strong and specific anatomical connections between the ACC and the LPFC, which may mediate cognitive interactions (Medalla and Barbas, 2010). The relationships between evaluative functions in the ACC and executive functions in the LPFC would account for rapid behavioral adaptation.

SUMMARY

Sensory processing has divergent streams for different goals: the lateral system for localizing and discriminating sensory stimuli, and the medial system for obtaining affective and motivational values. There is a wealth of evidence that the medial pain system, the core stations of which include the PAG, medial thalamus, and ACC, processes noxious inputs and generates negative affect. The medial pain system may complement the dopamine system, which processes reward value and generates prediction error signals. The PAG is thought to be involved in automatic responses such as freezing. The amygdala-OFC system plays a key role in aversive association learning. This system may enable the anticipation of harmful events based on their predictors. The amygdala-OFC system may also contribute to appetitive association learning. In addition to its role in pain perception, the ACC generates feedback signals that are triggered by behavioral errors and negative reinforcements. The feedback signals emerge as ERNs, which may reflect negative prediction errors. The ACC-LPFC connections appear to bridge the medial and lateral pathways by sending feedback signals generated in the medial pathway to control the ongoing cognitive processes in the lateral pathway.

PERSPECTIVES

Pain and pleasure may be two sides of the same coin. How the brain treats the opposing signals is an important question that remains to be unanswered. The common currency theory

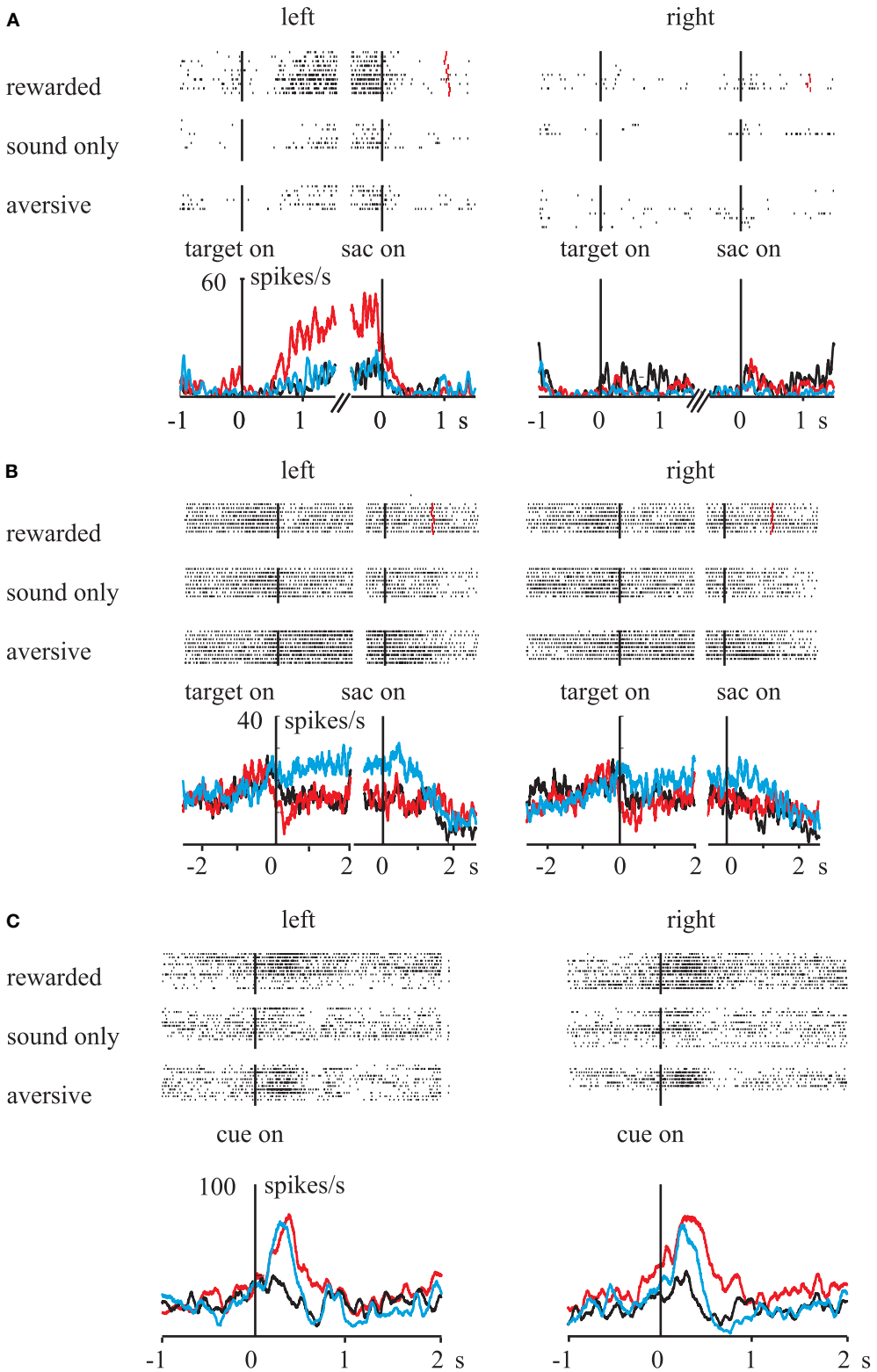

FIGURE 3 | Influences of rewarding and aversive outcomes on activity in the primate LPFC. Raster-histograms of different types of single neurons are displayed. **(A)** The activity of this neuron increased during rewarded trials when the saccade target was presented in the left visual field. **(B)** This neuron exhibited higher delay-period activity during aversive trials when the saccade target was on the left. **(C)** The activity of this neuron increased during both rewarded and aversive trials, independent of the target cue location. Red line, rewarded trials; black line, neutral trials; blue line, aversive trials. Vertical lines indicate the onset of the events: target on, onset of the spatial cue for future saccade; sac on, saccade onset; cue on, onset of the reinforcement cue. Reprinted with permission from Neuron (Kobayashi et al., 2006).

provides a simplistic view that various kinds of rewards are converted into a value measure (Montague and Berns, 2002). Whether aversive learning is explained in this framework remains to be elucidated.

In addition to theoretical interest, research into the aversive system has clinical implications for pain treatment. A greater understanding of the pharmacological and physiological mechanisms underlying the aversive system is essential for the advancement of therapeutic approaches to pain (Nguyen et al., 2011).

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Pain, decisions, and actions: a motivational perspective

Katja Wiech* and Irene Tracey

Nuffield Division of Anaesthetics, Nuffield Department of Clinical Neurosciences, Centre for Functional Magnetic Resonance Imaging of the Brain, John Radcliffe Hospital, University of Oxford, Oxford, UK

Edited by:
Ben Seymour, University of Osaka, Japan

Reviewed by:
Lauren Atlas, New York University, USA
Mathieu Roy, University of Colorado Boulder, USA

****Correspondence:***
Katja Wiech, Nuffield Division of Anaesthetics, Nuffield Department of Clinical Neurosciences, Oxford Centre for Functional Magnetic Resonance Imaging of the Brain, John Radcliffe Hospital, University of Oxford, Oxford OX3 9DU, UK.
e-mail: katja.wiech@ndcn.ox.ac.uk

Because pain signals potential harm to the organism, it immediately attracts attention and motivates decisions and action. However, pain is also subject to motivations—an aspect that has led to considerable changes in our understanding of (chronic) pain over the recent years. The relationship between pain and motivational states is therefore clearly bidirectional. This review provides an overview on behavioral and neuroimaging studies investigating motivational aspects of pain. We highlight recent insights into the modulation of pain through fear and social factors, summarize findings on the role of pain in fear conditioning, avoidance learning and goal conflicts and discuss evidence on pain-related cognitive interference and motivational aspects of pain relief.

Keywords: pain, modulation, goals, learning, motivation, analgesia, cognitive, affective

INTRODUCTION

Of the various consequences our actions can have, pain is probably the strongest indicator that our behavior needs readjustment. Joint pain after a first running session, for instance, indicates that we might have to slow down, start with a shorter distance or improve our running style. Pain therefore motivates decisions and actions to prevent further harm to the organism. Its imperative character has made pain a popular tool in studies investigating different aspects of learning. The vast literature on classical and operant conditioning is difficult to imagine without noxious stimuli driving the acquisition and shaping of new behavior. More recently, noxious stimuli have also been employed in studies on other basic psychological processes such as value representation and decision-making in which pain features as an opponent to reward stimuli.

However, action implications of pain have also become the focus of research on pain itself. Pain commonly triggers withdrawal behavior that might be adaptive in acute situations but can be maladaptive if it becomes excessive. Persistent avoidance behavior in which patients, for instance try to prevent or alleviate pain by reducing physical activity, is associated with long-term negative affective outcome and, ironically, often leads to more pain. Behavioral consequences of pain (including non-overt cognitive and affective behavior) can therefore directly contribute to the maintenance of chronic pain. In contrast to research in which pain is used as a tool to investigate general principles of learning or decision-making, these investigations aim at characterizing pain-related decision and actions with a focus on their repercussions for the perception of (clinical) pain.

Last but not least, pain not only motivates behavior but is also subject to and influenced by motivational states. The same joint pain we experienced during our first running session might be negligible if it occurred while we try to escape from an assailant. The relationship between pain and motivations is therefore considered bidirectional. Over recent years, interest in the modulation of pain through cognitive and affective processes has intensified considerably and constitutes a third strand of research—this time, however, with a focus on sensory processing. Due to studies in this and related fields, pain is no longer seen as a direct reflection of incoming nociceptive information but is understood to vary depending on cognitive-affective influences, including current and long-term motivations of the individual.

For all three lines of research, behavioral studies have extensively characterized the psychological processes involved and neuroimaging studies have begun to elucidate their underlying neural basis. In most cases, these studies were able to describe neural correlates and identify brain regions that are pivotal to the respective process. However, more research is needed to depart from this rather descriptive approach and understand the neural mechanisms underlying the interaction between pain, decisions, and actions.

In this article, we will give an overview on the existing behavioral and neuroimaging literature on this interaction, introduce key theoretical concepts and models, portrait new emerging lines of research and highlight open questions that warrant further attention. In particular, we will discuss findings from neuroimaging studies investigating (1) the role of pain in fear conditioning, (2) avoidance behavior in the context of pain, (3) pain-related goal conflicts, (4) the interruptive function of pain on cognitive processes, and (5) the influence of motivational states on the perception of pain.

INFLUENCE OF PAIN ON DECISIONS AND ACTIONS

PAIN AS A PRIMARY REINFORCER IN ASSOCIATIVE LEARNING

Studies investigating learning (and particularly associative learning during fear conditioning) have widely capitalized on the fact

that pain motivates behavior. In fear conditioning, an individual is exposed to an initially neutral stimulus (e.g., geometric shape; conditioned stimulus, CS) that is paired with an aversive stimulus (e.g., noxious heat; unconditioned stimulus, US). As the individual learns that the CS predicts the US, the CS acquires aversive properties and is able to elicit conditioned fear responses.

Studies using formalized computational models such as the Rescorla–Wagner model or temporal difference learning have begun to elucidate the mechanisms that underlie learning. Based on numerous observations, these models assume that learning is primarily driven by the informational value of the unconditioned stimulus (US), i.e., it is enhanced when the CS is paired with an unexpected as opposed to an expected US. Critically, a discrepancy between the expected and the experienced US generates a "prediction error signal" in the brain that triggers updating of expectations (for an overview see McNally et al., 2011). Using functional magnetic resonance imaging (fMRI), Ploghaus et al. (2000) provided first evidence for both positive and negative prediction error signals in pain-related learning. Unexpected pain led to increased activity in the hippocampus, superior frontal and superior parietal lobe as well as in the cerebellum. The unexpected omission of pain, in contrast, increased the signal level in these regions except for the superior frontal lobe that showed reduced activity.

Temporal difference learning in the context of pain has been shown by Seymour and colleagues. In a second-order cue learning task, participant were presented with two consecutive visual cues that predicted the application of a high or low-intensity noxious stimulus (Seymour et al., 2004). On some of the trials, the expectation that had been induced by the first cue was revised by the second cue that was fully predictive in all trials. Prediction error processing following cue update was reflected in increased activation in the anterior insula and the ventral striatum. In a second study using a classical conditioning paradigm in healthy volunteers in which visual cues predicted the termination of tonic pain, Seymour et al. (2005) showed that learning about pain relief follows reward-like learning signals found in the amygdala and midbrain. The exacerbation of pain, in contrast, could be described by aversion-like signals in the orbitofrontal and anterior cingulate cortices. In a recent study, the same authors investigated prediction error processing in a decision-making task (Seymour et al., 2012). On each trial, participants had to choose one of four options, which were associated with different probabilities to receive monetary reward or a noxious stimulus. Pain-related prediction error processing was negatively correlated with activation of the striatum while the reward-related prediction error showed a positive correlation with activation in the same region.

Experimental studies on fear conditioning commonly use exteroceptive stimuli such as visual or auditory stimuli as the CS. These stimuli are deliberately chosen to be abstract and neutral (e.g., abstract shapes or white noise) as they are intended to only become meaningful (i.e., predictive) through the association with the US. In many clinical conditions including anxiety disorders and chronic pain, however, symptoms are more commonly predicted by natural interoceptive and proprioceptive stimuli. Interoceptive stimuli provide afferent information from receptors that monitor the internal state of the body, e.g., migraine aura, stiff joints, or a general feeling of discomfort. Interoceptive fear conditioning therefore occurs when an association between an interoceptive CS and a US (e.g., pain) has been established (De Peuter et al., 2011). Despite its clinical relevance, interoceptive conditioning and its role in the development and maintenance of chronic pain has only received very little attention so far.

First studies, have, however, begun to explore the influence of proprioception that is defined as the perception of posture and movement. Proprioceptive fear conditioning is particularly relevant in patients with pain in the musculoskeletal system. Fear of movement, for instance, is a strong predictor of self-reported disability (Crombez et al., 1999). In a recent study, Meulders et al. (2011) demonstrated the acquisition of fear of movement-related pain through associative learning in healthy subjects. In a fear conditioning paradigm, a particular joystick movement served as a conditioned stimulus (CS) that was followed by a painful electrical stimulus (CS+). A second movement was not associated with the noxious stimulation (CS−). Over time, the CS+ movement started to elicit a conditioned fear response, as indicated by fear-potentiated eyeblink startle responses and increased fear of pain ratings following the CS+ movement. Longer response latencies for CS+ movements suggest that as a consequence participants became more reluctant to initiate the CS+ movement or were inclined to avoid the CS+ movement.

In a first attempt to investigate neural responses induced by proprioceptive cues, Barke et al. (2012) presented chronic low back pain (CLBP) patients and healthy controls with pictures showing back-straining or neutral movements. As expected, the patient group rated the back-straining pictures as more negative and arousing. However, brain responses acquired with fMRI did not reveal any group differences in the interaction analysis. Holtz et al. (2012) used fMRI to investigate the anticipation of a hyperventilation task as an interoceptive threat. When healthy subjects were presented with a visual cue that signaled the hyperventilation task, increased activation was found in the anterior insula, orbitofrontal cortex (OFC) and mid cingulate cortex (MCC), resembling findings on the anticipation of exteroceptive stimuli (e.g., Wiech et al., 2010).

Despite its long-standing history, research on associative learning and its relevance for chronic pain will remain a topic of interest with many facets. In addition to learning about interoceptive and proprioceptive cues discussed above, associated research lines have, for instance, begun to explore the generalization of fear responses to stimuli that resemble the CS (Lissek, 2012) or aim at understanding extinction learning to improve therapeutic interventions targeting learned maladaptive responses (Milad and Quirk, 2012).

PAIN AND AVOIDANCE LEARNING

Learning about cues that predict pain enables us to avoid pain before it occurs. The clinical syndrome termed asymbolia that is characterized by a blunted reaction to pain and the lacking motivation to avoid or reduce pain exemplifies the biological significance of this motivational component. Patients with pain asymbolia commonly present with severe injuries that not only relate to the initial trauma but also to the lack of subsequent protective behavior as the physical harm does not

trigger actions that are required to restore physical integrity. Although avoidance behavior might be beneficial in acute situations, it can be detrimental if it becomes excessive. For chronic pain patients, excessive avoidance behavior has been shown to exacerbate pain (see Vlaeyen and Linton, 2000; Leeuw et al., 2006 for review) and the degree of avoidance behavior is a strong predictor of pain-related disability (Karsdorp and Vlaeyen, 2009).

According to psychological models, the maintenance of avoidance behavior can mainly be explained by its ability to reduce fear. Because pain-predictive cues trigger fear and anxiety, avoiding these cues promises the escape from these negative emotional states. The aim of avoidance strategies is therefore not only to prevent pain but to avoid the aversive anticipatory state associated with it. The dual process theory (Mowrer and Lamoreaux, 1946) therefore posits that avoidance learning comprises two stages: the initial phase in which we learn about predictive cues through associative learning and the second phase in which avoidance behavior is reinforced and maintained by fear reduction following the principles of operant conditioning. Critically, avoidance behavior minimizes the opportunities to learn that the feared stimulus or event is no longer associated with pain—an implication that makes avoidance behavior particularly resistant to extinction. A key intervention in cognitive behavioral therapy (CBT) approaches to avoidance behavior is therefore the exposure to feared stimuli or events to break the vicious circle of avoidance and symptom maintenance.

Experimental studies approach avoidance learning by investigating responses to cues that predict the omission or absence of adverse outcome. Neuroimaging studies using this paradigm have shown that avoidance learning critically involves the amygdala (Schlund and Cataldo, 2010; Prévost et al., 2011). The presentation of cues that signaled the possibility to avoid future money loss or escape from immediate escalating money loss both led to increased activation of this structure (Schlund and Cataldo, 2010). Although additional brain regions such as the striatum and hippocampus have been implicated in avoidance learning (Schlund et al., 2011), their role is considerably more controversial.

Intriguingly, the neural circuitry underlying avoidance learning substantially overlaps with the one underlying approach learning. Visual cues that signal trials of potential monetary gain and those signaling avoidance of monetary loss both induced increased activation in prefrontal regions, insula, anterior cingulate cortex (ACC), amygdala, hippocampus, and parahippocampus (Schlund et al., 2011). This strong resemblance of activation patterns has led to the hypothesis that similarly to positive outcome, avoidance might be rewarding. Support for this notion comes from studies investigating brain responses during the presentation of choice outcome. Delivery of monetary reward and the omission of monetary loss were associated with comparable activations in frontal and striatal regions (Schlund et al., 2011). In a study by Kim et al. (2006), participants performed an instrumental choice task, in which on each trial they had to choose one of two actions in order to either win money or avoid losing money. Activation in the medial OFC, a region that has been previously implicated in encoding stimulus reward value, was increased following the delivery of the reward, but also following successful avoidance of monetary loss.

From a clinical perspective, it seems noteworthy that although avoidance behavior prevents patients from encountering the feared outcome (e.g., pain), it—ironically—leads to heightened fear and catastrophic thinking in the long-term (Craske et al., 1989; Eifert and Heffner, 2003). In line with this notion, fear-related activation in the amygdala and insula seem to be maintained even when aversive outcome is avoided (Schlund et al., 2010), confirming that avoidance preserves rather than erases fear.

Taken together, studies on avoidance learning suggest that avoidance behavior might have a rewarding component that could explain its maintenance, even if it is associated with high costs—an aspect we will explore in the next section. It should be noted that in studies on avoidance learning, aversive outcome has so far commonly been operationalized as loss of monetary reward or absence of gains to allow for direct comparison of positive and negative outcome (i.e., gain vs. loss of money). Whether findings from these studies can directly be translated to the delivery of aversive stimuli such as pain and on a more general level to avoidance behavior related to acute and chronic pain warrants further investigation.

Although to date research on avoidance behavior has mainly focused on learning, related aspects could aid in understanding the motivational basis of this behavior and its common resistance to extinction. For instance, dispositional inter-individual differences in exploratory behavior that might be determined by personality or genotype could add a relevant piece to the puzzle of understanding and targeting excessive avoidance behavior. Furthermore, contemporary theories on action selection suggest that our behavior is governed by at least two systems, a goal-directed system and a habitual system (see Rangel et al., 2008 for review). Avoidance behavior might require different intervention strategies, depending on the system driving it. If the behavior is goal-directed (or "model-based," see Daw and Shohamy, 2008 for details), it could be targeted by challenging its underlying beliefs—an approach that is, for instance, indicated when avoidance behavior is driven by exaggerated irrational beliefs. In contrast, if the behavior is habitual, it might subsist despite successful treatment of pain that caused the avoidance behavior.

GOAL CONFLICT IN THE CONTEXT OF PAIN

Although avoidance behavior might help in reducing pain on the short-term, it is often associated with immediate and long-term costs. Giving up on the plan to watch a movie at the cinema might spare one the back pain from sitting in an uncomfortable chair but also deprives from the pleasure of spending time with friends. Moreover, conflict can also arise from approach behavior. For instance, because long-term consumption of certain analgesics is known to increase the risk of side effects, the momentary pain relief has to be compared against the health risk associated with consumption of the analgesic. The urge to avoid pain can therefore compete with other interests we have. Of note, the perception of goal conflict itself can be distressing and might even contribute to symptom exacerbation (Hardy et al., 2011).

Contemporary models of goal-directed choices (e.g., Rangel and Hare, 2010) posit that the decision whether to pursue an action (e.g., pursuing physical activity in the presence of pain) or not depends on the value of this action that results from the difference between the value of the outcome that is generated by each action (e.g., pleasure experienced during physical activity) and the associated costs (e.g., increase in pain).

There is now solid evidence from numerous studies in animals and humans showing that stimulus evaluation as the first part of this equation critically depends on a region comprising parts of the ventromedial prefrontal cortex (VMPFC) and orbitofrontal cortex (OFC; see Levy and Glimcher, 2012). Interestingly, the OFC seems to be concerned with the evaluation of appetitive stimuli as well as aversive stimuli (Plassmann et al., 2010; Morrison and Salzman, 2011).

Experiments exploring the relevance of costs commonly investigate changes in the evaluation of desired outcome (e.g., monetary reward) when it co-occurs with aversive outcome such as loss of money or delivery of noxious stimuli. In a study by Talmi et al. (2009), participants had to choose between monetary reward that was associated with a low or high probability to receive a mild or strong electric shock. Their results show that although the OFC still signaled the reward value of expected payment, activation in this region was attenuated the stronger the expected noxious stimulation, suggesting that the OFC integrates costs into stimulus evaluation. This integrative mechanism was recently studied in more detail using a computational modeling approach in which behavioral data (i.e., response times and choice behavior) were employed to inform the analysis of neuroimaging data (Park et al., 2011). As in the study by Talmi and colleagues, participants could accept or reject offers that consisted of a combination of different amounts of monetary reward and pain of different intensity levels. Neuroimaging data in combination with computational modeling confirmed that both outcomes are considered in an interactive (non-linear fashion) in the OFC but also in the subgenual anterior cingulate cortex (sACC) and dorsolateral prefrontal cortex (DLPFC), suggesting that these regions integrate information about costs (e.g., pain) into the evaluation of expected benefits (i.e., money).

Although the prospect of pain can trigger avoidance behavior and it is often tempting to even abandon previously valued activities because they might lead to pain, we are sometimes able to "stay on task" (Seminowicz and Davis, 2007a) or pursue potentially pain-related activities despite the pain. In these cases, the value of an activity seems to outweigh the gain of pain avoidance. This suggests that higher-level goals such as the long-term outcome of a decision can influence the decision-making process and might even be considered at the stage of action value calculation. First evidence for such a top–down influence on stimulus or action evaluation comes from a study in which participants had to choose between healthy and unhealthy food of varying palatability (Hare et al., 2009). As in previous studies, the evaluation of the food engaged the VMPFC/OFC. However, trials in which participants opted for the healthy food were also characterized by increased activation in the DLPFC—the key region for top–down cognitive control. Most importantly, the engagement of the VMPFC during the presentation of liked-but-unhealthy food was reduced as a function of DLPFC involvement during these trials, suggesting that value encoding in the VMPFC is sensitive to input from a brain region representing higher-order goals.

To summarize, there is cumulative evidence suggesting that the prospect of pain is integrated into the evaluation of appetitive stimuli and might thereby affect the net evaluation of these stimuli. The translation of this experimental research in healthy volunteers into patients suffering from chronic pain could provide novel, clinically highly relevant insights into pain-related choices and more specifically, the compromised ability to implement top–down processing in goal conflicts. A particularly promising focus is the characterization of impaired DLPFC functions, which comprise not only a top–down influence on stimulus and action evaluation but also executive functions such as "goal shielding" through biased attentional processing. Furthermore, future neuroimaging studies on pain-related goal conflicts should consider other conflict-relevant dimensions apart from valence. In contrast to experimental settings in which participants choose between simple stimuli that are delivered immediately, conflict in the context of (chronic) pain often arises from more complex scenarios in which the options are typically on different time scales (e.g., pain relief from analgesics as short-term benefit vs. side-effects as long-term adversity). Insights into the integration of action outcome with different time constants could help in understanding the preference for immediate pain relief despite the detrimental long-term costs. Finally, future studies on the resolution of goal conflicts in the context of pain should explore the integration of relevant information in the brain in more detail. The exchange and comparison of information regarding costs and benefits as well as the subsequent decision-making processes require dynamic brain circuitries rather than single brain regions. Tools focusing on dynamic parameters (e.g., analysis of functional connectivity) and computational models that inform brain imaging analysis based on behavioral data can therefore add valuable new insights.

INTERRUPTIVE FUNCTION OF PAIN: ATTENTIONAL PROCESSES

Although top–down influences can aid in protecting goals unrelated to pain, they have to allow for vital information to enter awareness in order to ensure survival. Because of its biological relevance, pain is often prioritized over concurrent activities and can therefore disrupt ongoing cognitive processes (see Eccleston and Crombez, 1999 for review). In experimental studies, this interruptive function of pain is reflected in compromised accuracy and speed in cognitive tasks (e.g., Stroop task, dot-probe, primary task paradigm) when the task is performed during concomitant noxious stimulation in comparison to a condition in which the task is performed without noxious stimulation (Crombez et al., 2012; Moore et al., 2012).

In order to understand the disruptive effect of pain, we have to consider the way the brain copes with simultaneous attention-demanding processes. Contemporary models of attention hold that our attentional capacity is limited (Lavie, 2005) and concomitant cognitive processes compete for attentional resources. Highly demanding or prioritized processes would thereby engage full capacity in relevant processing and leave no spare capacity to other processes.

A number of findings from neuroimaging studies support the notion that a competition for common resources accounts for the interruptive function of pain. First, some brain regions including the prefrontal cortex, primary and secondary somatosensory cortex, rostral ACC, anterior insula, and cerebellum can be sensitive to both operations (Wiech et al., 2005; Seminowicz and Davis, 2007a). Second, the effect of pain on concomitant cognitive processes is most prominent the higher the pain intensity and the more difficult the task. While mildly and moderately painful stimuli often have no or only minor effects (Seminowicz and Davis, 2007a), more severe pain that is more likely to attract attentional resources can increase error rates (Wiech et al., 2005). In line with this observation, Buhle and Wager (2010) showed that the degree to which pain compromises task performance is directly proportional to the perceived intensity of pain on a trial-by-trial basis. These findings suggest that the increased demand for attentional resources when the task is performed under pain can be compensated for until no more resources can be allocated; then the lack of resources becomes apparent as either compromised task performance or attenuated pain perception.

Attentional resources are allocated to perceptual processes based on the salience of the incoming information as well as the relevance of the information for prioritized goals (for review see Legrain et al., 2009). Stimulus salience that is defined as the ability of a stimulus to stand out relative to other stimuli (Yantis, 2008) is highest for novel, intense and potentially threatening stimuli and commonly triggers bottom–up mechanisms of attention selection. Bottom–up attentional processes have mainly been related to the anterior insula and MCC and the salience network described above. Importantly, the anterior insula as the central hub of the salience network is connected to the cognitive control network. This network consists of the DLPFC and the posterior parietal cortex (PPC) and governs cognitive functions such as attention allocation, working memory and decision-making (for review see Katsuki, 2012). Once a stimulus has been detected as salient, the anterior insula activates the cognitive control network (Sridharan et al., 2008) and thereby facilitates task-related information processing. In other words, the anterior insula ensures that salient stimuli such as painful stimuli will have preferential access to the brain's attentional and working memory resources (Menon and Uddin, 2010). Moreover, the anterior insula decreases activity in the "default mode network, DMN" (Sridharan et al., 2008) that comprises the VMPFC and posterior cingulate cortex (PCC) and shows decreased activation during sensory or cognitive processing. Although the relevance of DMN modulation for selective attention is less well understood, there is evidence showing that failure of this DMN regulation through the anterior insula leads to inefficient cognitive control (Bonnelle et al., 2012). In line with these findings, patients with CLBP (Loggia et al., 2012) and those with fibromyalgia (Napadow et al., 2010) show a heightened functional connectivity between the anterior insula and the DMN that decreased with successful pain treatment in fibromyalgia patients (Napadow et al., 2012). Fibromyalgia patients in whom pain often co-occurs with cognitive impairments also showed an increased functional connectivity between the anterior insula and the cognitive control network that exhibits increased engagement during attention-demanding operations, including pain. In healthy individuals, a increased attentional demand as, for instance, during task performance under pain, can be accommodated for by an increase in the engagement of the cognitive control network that ensures consistent performance despite the pain (Seminowicz and Davis, 2007b). Although speculative at the moment, it is conceivable that this ability is compromised by the overriding influence of the anterior insula that prioritizes the more threatening operation.

The allocation for attentional resources, however, not only depends on stimulus salience but also on internal goals that are implemented by top–down signals from the cognitive control network, predominantly in the DLPFC as described above. Through the allocation of attentional resources, this system ensures focused attention on goal-relevant stimuli while responses to distractors in the presence of relevant stimuli are suppressed.

Importantly, pain not only interferes with the performance of cognitive operations but can also hamper concomitant perceptual processes. Using fMRI, Bingel et al. (2007) investigated the influence of concomitant application of noxious stimuli on visual processing. In this study, laser stimuli of different intensities were applied during performance of a working memory task (1- or 2-back task). The noxious stimulation lead to longer response times, particularly when the more demanding 2-back task had to be performed during high-intensity stimulation. In a subsequent surprise recognition task, participants showed lower recognition rates for pictures that had previously been presented with high-intensity stimulation. At the neural level, this interruptive effect of pain on task performance was reflected in impaired visual processing, as indicated by reduced activation in the lateral occipital complex during high pain.

To summarize, the high biological relevance of pain is likely to trigger the salience network that ensures prioritized processing through connections with the cognitive control network governing attention allocation. Although directing attention to pain is critical in acute situations to prevent further harm, it can lead to severe cognitive disability in chronic pain. Additional studies are needed to understand under which circumstances we are able to "stay on task" and how cognitive control regions ensure that we can disengage from pain. Coordinating demands and available resources requires communication between brain regions, which is likely to be reflected in dynamic parameters of a flexible network of brain regions. A more detailed understanding of the factors that guide the allocation of attentional resources could shed light on the over-prioritization of pain-related processes that is characteristic for many chronic pain syndromes and often interferes with the pursuit of goals unrelated to pain (see Van Damme et al., 2010). Inter-individual differences in the ability to recruit the top–down control might explain the different effects pain can have on task performance (Braver et al., 2010), including compromised task performance in some and improved performance in others (Seminowicz et al., 2004; Tiemann et al., 2010).

INFLUENCE OF MOTIVATIONAL STATES ON THE PERCEPTION OF PAIN

For centuries, the perception of pain had been conceptualized as a linear read-out of incoming nociceptive information: the more nociceptive information enters the sensory system, the stronger

the pain. However, over the recent years numerous studies have demonstrated that pain is substantially influenced by cognitive-affective processes, including motivational factors such as "fear of pain" or the prospect of pain relief. The following section will mainly focus on the influence of fear as one of the most basic motivations but will also highlight recent advances on the influence of social factors as a new, emerging field of research. For a discussion of other, more complex cognitive processes on pain, we refer the reader to two review articles (Wiech et al., 2008; Wiech and Tracey, 2009).

FEAR AND ANXIETY

Amongst the different motivational states, the influence of fear and anxiety on pain has probably most extensively been studied. Numerous behavioral studies have shown that fear generally leads to higher pain intensity ratings and reduced pain tolerance (see Wiech and Tracey, 2009 for review). Ploghaus et al. (2001) were the first to demonstrate that the increase in pain perception during an experimental manipulation of anxiety leads to amplified processing in pain-related brain regions, including the insula and cingulate cortex which can be considered "target" regions of the anxiety-related modulation of pain. Subsequent studies focusing on cognitive aspects of fear and anxiety such as expectation, anticipation, or catastrophizing extended this finding. The expectation of high-intensity pain resulted in increased activation in pain-related brain regions during stimulus receipt relative to low-intensity expectation, despite physically identical stimulation (Koyama et al., 2005). Moreover, stimulus-related brain responses can be predicted based on the level of activation during the preceding anticipation period (Fairhurst et al., 2007; Ploner et al., 2010). Although the experimental manipulation used in these studies differ, they are all aimed at varying the threat or interruptive value of pain.

So far, only a few studies have aimed at identifying brain regions that might be involved in mediating the effect (i.e., "sources" of modulation). During stimulus application, the expectation of a high-intensity stimulus is associated with increased activation of the (para)hippocampal regions (Ploghaus et al., 2001; Gondo et al., 2012) and individuals who are sensitive to anxiety-inducing cues show stronger hippocampal activation during stimulus anticipation and receipt than those who are less cue-sensitive (Ziv et al., 2009). More importantly, the (para)hippocampal formation seems to be related to anxiety produced changes in activity in pain-related brain regions (i.e., ACC and mid/posterior insula) during a more threatening condition (Ploghaus et al., 2001). Similarly, activation in the hippocampal formation (and ventral tegmental area of the brainstem) predicted insular activity during stimulus delivery (Fairhurst et al., 2007). Furthermore, the hippocampus might also be involved in nocebo effects (Kong et al., 2008; Bingel et al., 2011). When healthy volunteers were instructed that the withdrawal from the potent analgesic remifential could amplify pain perception, the reported increase in pain ratings scaled with increased activation in the left hippocampus (Bingel et al., 2011). Together, these findings suggest that the hippocampal formation may "tune" the sensitivity of brain regions involved in pain processing in a context-dependent manner. This notion is in accordance with the Gray-McNaughton theory on the hippocampal function in fear and anxiety (Gray and McNaugthon, 2000) that posits that the hippocampus amplifies neural representations of aversive events in order to bias the organism toward a behavior that is most adaptive to the worst possible outcome, as stated in Ploghaus et al. (2001).

A fear-related modulation of pain regions through a change in communication between brain regions has also been shown for the anterior insula (Wiech et al., 2010). As mentioned in the section on the interruptive function of pain, the anterior insula ensures that salient stimuli such as painful stimuli will have preferential access to mental resources. Together with the MCC, it is a key node of a network that predominantly responds to salient stimuli (Seeley et al., 2007; Franciotti et al., 2009; Taylor et al., 2009). Importantly, the directive influence of the anterior insula is sensitive to momentary perceptions of fear and anxiety. Contextual information about the threat value of an upcoming, potentially painful stimulation, for instance, engages the anterior insula which increases its functional connectivity with the MCC while participants are awaiting the stimulation (Wiech et al., 2010). Importantly, participants who subsequently showed a higher tendency to rate ambiguous stimuli as painful were characterized by a stronger activation in the MCC during stimulus receipt, indicating that the "tuning" of the MCC is perceptually relevant. In keeping with the notion of the anterior insula as a central hub for the amplification of pain through fear and anxiety the change in functional connectivity between the anterior insula and the periaqueductal grey (PAG) as a key region of the descending pain inhibitory network was found to depend on the trait anxiety of participants during an experiment examining how pre-stimulation brain activity predicts whether near threshold stimuli are perceived as painful or not (Ploner et al., 2010). The pivotal role of the anterior insula in the modulation of pain through fear and anxiety was also confirmed in a formal mediation analysis that identified the anterior insula (and other regions) as critical for cue-related effects on pain perception (Atlas et al., 2010). In sum, these studies indicate that the anterior insula connects to regions involved in pain processing (e.g., MCC) and modulation (e.g., PAG) in a flexible, context-dependent fashion.

In addition to hippocampal regions and anterior insula, studies in chronic pain populations emphasize the role of prefrontal areas in fear and anxiety-related modulation of pain, albeit with a considerable variation in prefrontal location. During the anticipation of pain as a cognitive element of fear and anxiety, patients with Irritable Bowel Syndrome (IBS) showed increased activation in the ventrolateral prefrontal cortex (VLPFC; Lee et al., 2012) while increased activation in the dorsolateral aspect of the prefrontal cortex (DLPFC) was found in fibromyalgia patients relative to healthy controls (Burgmer et al., 2011). The DLPFC is known to orchestrate cognitive processes such as selective attention, working memory or emotion regulation by connecting to brain regions that are relevant for these processes. The VLPFC, in contrast, has mainly been implicated in emotion regulation (Mitchell, 2011). In line with this notion, Jensen et al. (2012) recently showed that a reduction in anxiety through CBT correlated with an increase in VLPFC activation in fibromyalgia patients. In addition to functional changes, chronic pain patients

also show fear and anxiety-related structural alterations in prefrontal areas. For instance, patients with Complex Regional Pain Syndrome (CRPS) exhibit increased white matter connectivity between the VMPFC and nucleus accumbens (NAc) that was related to heightened anxiety (Geha et al., 2008).

Although fear and anxiety generally increase the perception of pain, the opposite effect can be found when these emotions exceed a certain level. From a motivational perspective, this so-called stress-induced analgesia is of particular interest because it demonstrates that pain can also be subject to priority considerations similarly to cognitive processes that can be disrupted by pain, as discussed above. If the individual is faced with challenges that are biologically more relevant than pain (i.e., survival in an acutely threatening situation) pain is perceived as less intense. Stress-induced analgesia is predominantly mediated by opioidergic mechanisms, as also reflected by the engagement of brain regions known to be part of the opioid-dependent descending pain inhibitory system, such as the rostral ACC (Yilmaz et al., 2010), but it also involves non-opioidergic (e.g., endocannabinoid) processes (Hohmann et al., 2005).

Despite recent advances in this field, additional studies are needed to understand the complex interaction between fear/anxiety and pain processing in more detail. First, a growing number of observations on the role of the (para-)hippocampal formation in pain modulation has to be integrated into the vast body of literature on this structure in fear and anxiety in general. Furthermore, the significance of this structure for pain-related and fear-related disruption of cognitive operations as discussed in the section on the interruptive function of pain warrants further investigation. For instance, a recent study showed that the pain-related disruption of memory encoding was reflected in the hippocampus (Forkmann et al., 2013), suggesting that this structure is not only a mediator of pain modulation but might also be a target. Although the hippocampus is often considered a single functional entity, there is cumulating evidence suggesting a functional segregation into a dorsal part related to cognitive functions and a ventral part that is involved in emotional processing and stress (for an overview see Fanselow and Dong, 2010) which also show differential functional connectivity patterns under threat (Satpute et al., 2012). The investigation of the role of both subdivisions in pain-related fear and anxiety could reveal a more detailed picture of the relevance of the hippocampus in the modulation of pain.

Second, although a wealth of animal studies has highlighted the relevance of brainstem structures such as the PAG and VTA in fear-related pain modulation, precise insights into their role in human pain models are relatively sparse. However, the repeatedly found involvement of these structures in studies on cognitive-affective aspects in healthy volunteers (Bantick et al., 2002; Tracey et al., 2002; Dunckley et al., 2005; Fairhurst et al., 2007; Ploner et al., 2010; Brodersen et al., 2012; Buhle et al., 2012), human models of central sensitization (Iannetti et al., 2005; Zambreanu et al., 2005; Lee et al., 2008; Wanigasekera et al., 2011) and chronic pain patients (Berman et al., 2008) points toward an equally critical role in humans. Second, studies outside the pain field have emphasized the significance of the amygdala and its dynamic interaction with prefrontal regions in fear and anxiety (Bishop, 2007). Although a recent study suggested a decrease in amygdala activity as a robust indicator for successful emotion and pain regulation (Lapate et al., 2012), our understanding of amygdala function in human pain processing is still limited to its role in associative learning, whereas for animal studies it has a well characterized role in nociceptive processing (Neugebauer et al., 2004; Ji et al., 2010). Future studies should therefore investigate the translation of these animal models into humans. Third, the variability in findings on prefrontal cortex contribution warrants further investigation. Studies on the role of the prefrontal cortex in cognitive control and emotion regulation have, for instance, inspired hierarchical models whereby the lateral prefrontal cortex controls anxiety-related limbic activity through connections with the VMPFC (Klumpers et al., 2010). Studies with a focus on prefrontal function, probably probing its involvement in pain modulation using transcranial magnetic stimulation (TMS) could detail the notion of "keeping pain out of mind" (Lorenz et al., 2003) as the key function of the prefrontal cortex in pain modulation.

PLACEBO ANALGESIA, REWARD AND DOPAMINERGIC TRANSMISSION

The type of pain modulation that has probably most commonly been linked to motivational aspects is placebo analgesia. More specifically, it has been hypothesized that the ability to produce an analgesic effect via endogenous pain inhibitory mechanisms scales with the anticipation of reward from pain relief (for a more comprehensive view on placebo analgesia, including the role of the descending pain inhibitory pathway in mediating the influence of placebo-related beliefs, see Zubieta and Stohler, 2009; Tracey, 2010; Atlas and Wager, 2012). Using functional molecular imaging, Scott et al. (2007) investigated the relationship between reward anticipation and individual analgesic placebo responses in healthy volunteers. Their results showed that the degree of placebo analgesia correlated with the release of dopamine during placebo analgesia. Moreover, both measures were proportional to activation in the NAc during the expectation of monetary reward in a separate fMRI experiment, which indicates that variations in the function of reward processing might determine one's ability for endogenous pain control.

But what exactly is the link between the dopaminergic system and (endogenous) analgesia? There is evidence suggesting that dopamine itself might have analgesia properties and might affect nociceptive processing directly (for an overview see Jarcho et al., 2012). Another possibility, however, that has been proposed in the context of placebo analgesia as a form of endogenous pain modulation and that is of particular interest from a motivational perspective is the notion that dopaminergic NAc signal might be involved in the "encoding of the incentive value of the placebo, possibly acting as a gate or permissive system for the formation of placebo effects" (Scott et al., 2007). The expectation of reward (e.g., pain relief) triggers the release of dopamine in the NAc as the key structure of the ventral striatum. Studies on placebo effects in patients with Parkinson disease have shown that this expectancy-related release of dopamine in the ventral striatum precedes the release of dopamine in the dorsal striatum which leads to the placebo effect in patients with Parkinson disease

(de la Fuente-Fernández et al., 2002). Analogously, NAc dopamine release could drive the release of endogenous opioids, as recently proposed by Fuente-Fernández (de la Fuente-Fernández, 2009). Although experimental evidence for this pathway is still missing, placebo-induced dopaminergic NAc activity has been found to be positively correlated with the activation of the μ-opioid system in brain regions showing a placebo effect (Scott et al., 2008). Given the correlative nature of this finding, it is, however, difficult to discern whether the release of dopamine preceded or followed the release of opioids.

The relevance of the dopaminergic system for the modulation of pain has recently also been highlighted in a number of studies in chronic pain patients. Patients with fibromyalgia syndrome, for instance, showed reduced dopamine release following noxious stimulation in comparison to healthy controls (Wood et al., 2007). While the amount of dopamine release scaled with the perceived pain intensity in controls, such correspondence could not be found in the patient group. Furthermore, Geha et al. (2008) found substantial atrophy in the gray matter of the NAc in patients with CRPS patients. This finding is particularly interesting given that gray matter density in regions such as the ventral striatum (comprising the NAc) and prefrontal cortex is directly related to the degree of analgesia healthy volunteers experienced in a placebo paradigm (Schweinhardt et al., 2009). However, such changes are not consistent, as another study examining structural changes in patients with rheumatoid arthritis observed an increase in gray matter content in the basal ganglia, mainly in the NAc and caudate nucleus (Wartolowska et al., 2012). Finally, in a recent longitudinal study, Baliki et al. (2012) showed that the functional connectivity between NAc and prefrontal regions predicted the transition from acute to chronic back pain. Of note, it has recently been shown that mesolimbic dopaminergic regions including the NAc are controlled by the DLPFC (Ballard et al., 2011), linking reward processing and (placebo) analgesia to top–down control mechanisms that are involved in implementing higher-level goals.

Taken together, these studies suggest a critical role of dopaminergic reward-related brain regions and their interaction with the endogenous opioid system in pain modulation. However, direct evidence, for instance, from studies using dopamine antagonists in a placebo paradigm is still missing.

SOCIAL INFLUENCES

Although pain is a highly subjective and rather personal experience, it is sensitive to social influence. So far, the emerging strand of research on the influence of social factors on pain perception has mainly focused on two aspects: pain modulation through social support and social threat. Social support has been found to alleviate experimental and clinical pain, including labor, cardiac, and postoperative pain (see Brown, 2003 for an overview). In line with this change in pain intensity, participants exhibited less threat-related activation in various brain regions (including the anterior insula, DLPFC, and hypothalamus) when they were holding the hand of their spouse while they were awaiting a painful stimulation than when they were holding the hand of a stranger or in a non-hand-holding condition (Coan et al., 2006). Interestingly, this buffering effect was stronger the higher participants rated the quality of their marriage. In a recent study, Eisenberger et al. (2011) extended these observations to the period of pain receipt. Here, participants reported less pain when they were presented with a picture of their romantic partner during the application of the noxious stimuli. This modulatory effect was paralleled by increased activation in the VMPFC and as in the study by Coan et al. it scaled with perceived partner support. Moreover, activity in the VMPFC was related to decreased engagement of the dorsal anterior cingulate cortex (dACC) during pain receipt. Based on the association of the VMPFC with safety signaling (e.g., Klumpers et al., 2010) the authors concluded that social support might modulate pain via top–down regulatory mechanisms.

In comparison to this work on social support, the neural basis of the modulation of pain through social threat is less clear. Animal studies indicate that the relationship between social threat and pain perception might depend on the level of threat. In a study in mice, Langford and colleagues found reduced pain behavior in an experimental pain model when male animals were confined to close proximity to a stranger animal (Langford et al., 2011)—a finding that is in accordance with observations on stress-induced analgesia. However, when both animals were separated by metal bars that only allowed for partial physical contact and thereby reduced social stress, the same stimuli induced more pronounced pain behavior.

In addition to the level of threat, the effect of social threat also seems to depend on the perceived level of intentionality to cause harm. Physical harm that was caused by another person might be the result of an act of aggression or it might have occurred accidently. Interestingly, intentional harm is perceived as more severe and prevents habituation relative to non-intentional harm (Gray and Wegner, 2008; Peeters and Vlaeyen, 2011). Furthermore, the perceived intentionality seems to influence whether the (facial) expression of pain of the threatened individual corresponds to his perception of pain. Peeters and Vlaeyen (2011) showed that although intentional harm led to higher pain intensity ratings (relative to non-intentional pain) it reduced the facial expression of pain. The authors interpreted their finding within the framework of an evolutionary perspective on pain (Williams, 2002) that posits that the expression of pain also has a communicative function. In this view, the communication of pain aids in soliciting empathy and social support. However, it also discloses a level of vulnerability that might be exploited by less benevolent others to cause further harm. The suppression of pain expressions in the face of social threat might therefore be the more adaptive response if further intentional harm has to be feared.

Research on social influences on pain is still in its infancy but has already proven to add valuable insights into a more comprehensive view on pain [for an excellent overview on motivational and learning aspects of pain communication see Hadjistavropoulos et al. (2011)]. Future studies could aid in understanding the specific neurobiology underlying persistent pain states caused through interpersonal violence (e.g., from torture), which are known to be particularly resistant to treatment.

OUTLOOK

In this review, we have discussed two aspects that highlight the strong link between pain and motivations: the fact that pain motivates decisions and actions to prevent harm to the organism and the observation that pain, in turn, is also subject to motivations. Together, these findings encourage a functional perspective on pain that sees pain not only as a somatosensory experience but focuses on the various repercussions it has for cognitive, affective and social processes and considers its motivational aspects. The primary aim of most treatment approaches to chronic pain is the identification of pathological processes that cause or maintain the pain. Although this approach is successful in many cases, a large number of patients still suffer from pain that modern medicine has no sufficient relief or cure for. The observations discussed in this review show that research into the motivational aspects of pain is not only key to a better understanding of mechanisms that maintain or even cause pain, but because of their causal link to the development and maintenance of (chronic) pain they also offer promising ways to prevent and treat pain.

Over the recent years, considerable progress has been made in understanding motivational aspects of pain and identifying brain regions that are involved in these processes (for an overview see **Figure 1**). However, further research is needed to advance and refine these insights. First, studies need to go beyond the mapping of complex cognitive and psychological constructs to single brain areas and consider extended networks and their context-dependent dynamic reconfiguration. Advanced analysis techniques such as dynamic causal modeling allow for a detailed characterization of the cross-talk between brain regions, by specifying the direction of causation. Analyses of functional imaging data that are informed by results on the structural connectivity of relevant brain regions in the same individual will provide more insights into the individual capacity for pain modulation. Furthermore, recent advances in computational models can aid in characterizing relevant processes in more detail by using behavioral data such as response times to inform neuroimaging analyses.

Second, neuroimaging studies on motivational aspects of pain would benefit from the transfer and integration of findings on related topics, including fear and anxiety, decision-making, conflict resolution and goal-directed behavior. Research on anxiety, for instance, has shown that compromised prefrontal top–down processing underlies the attentional bias in high trait-anxious individuals (Bishop, 2009)—a mechanism that might also underlie biased attentional processing in chronic pain patients. Likewise, it has been shown that long-term

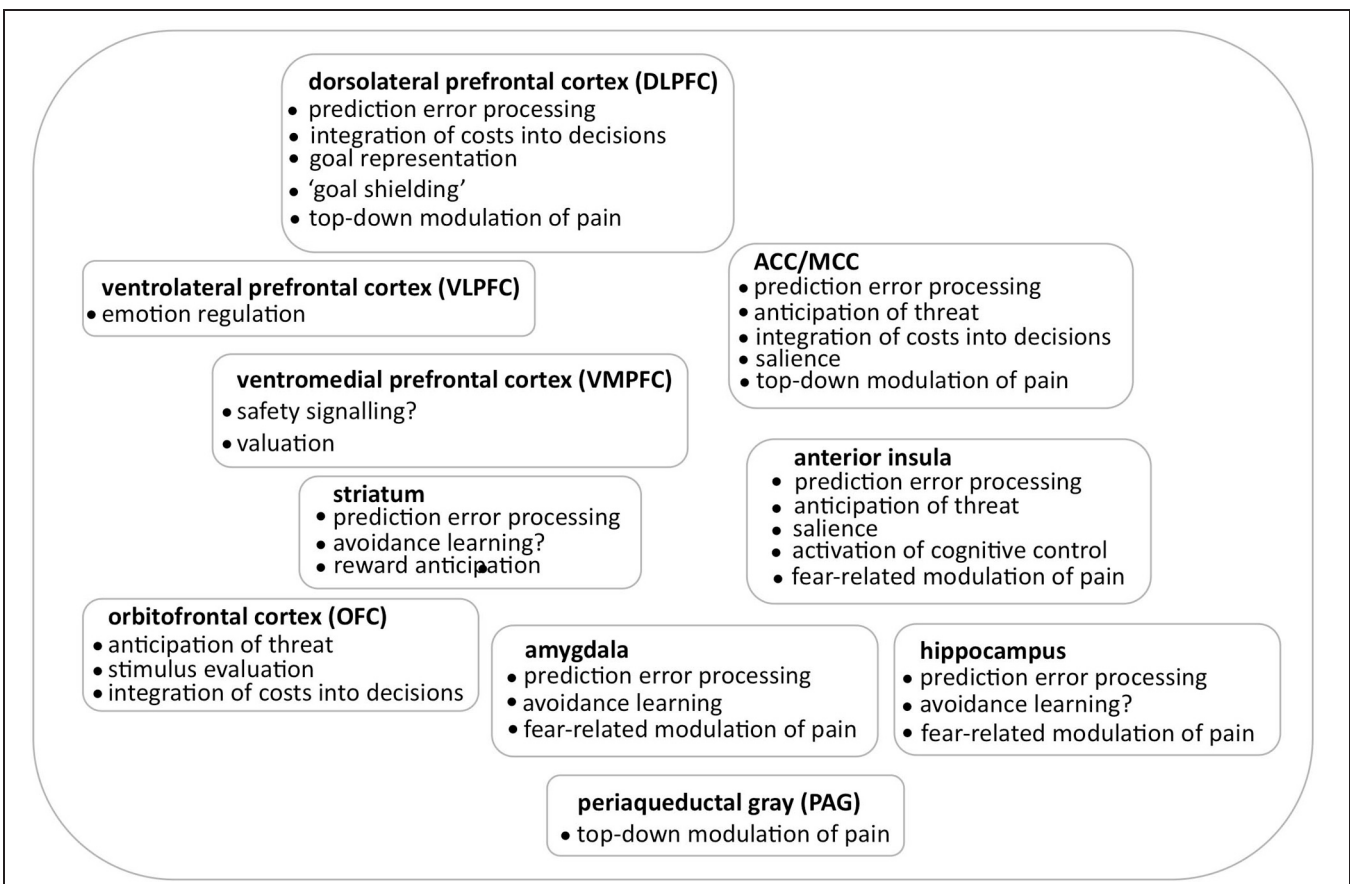

FIGURE 1 | Overview on the brain regions implicated in motivational aspects of pain.

consequences affect stimulus evaluation less than short-term consequences, a phenomenon termed temporal discounting. Similar processes might influence the decisions chronic pain patients make when comparing the immediate benefit of pain avoidance with the loss from missing out on previously valued activities.

Another aspect that has only received very little attention is the motor implications of pain. Pain undoubtedly motivates withdrawal behavior, particularly in acute situations, and drives behavior requiring motor responses in the chronic situation. Motor implications of pain are notoriously difficult to investigate using neuroimaging techniques, given the movement-related confounds they produce. However, understanding the (cognitive) demand of motor implications and their suppression could add a missing piece to the puzzle of pain.

Chronic pain remains one of the largest unresolved medical health problems in the developed world. A better understanding of how the brain responds in an adaptive and maladaptive way during the transition to and maintenance of chronic pain is key if we are to target these mechanisms for better patient management, pain relief and well being.

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The role of dopamine in the context of aversive stimuli with particular reference to acoustically signaled avoidance learning

Anton Ilango[1]*†, Jason Shumake[1,3], Wolfram Wetzel[1], Henning Scheich[1] and Frank W. Ohl[1,2]*

[1] *Leibniz Institute for Neurobiology, Magdeburg, Germany*
[2] *Institute of Biology, Otto-von-Guericke University, Magdeburg, Germany*
[3] *Department of Psychology, The University of Texas, Austin, TX, USA*

Edited by:
Philippe N. Tobler, University of Zurich, Switzerland

Reviewed by:
Shunsuke Kobayashi, Fukushima Medical University, Japan
Mitchell Roitman, University of Illinois at Chicago, USA

***Correspondence:**
Anton Ilango, Intramural Research Programme, National Institute on Drug Abuse, National Institutes of Health, 251 Bayview Blvd., Baltimore, MD 21224, USA.
e-mail: antonilango@hotmail.com; Frank W. Ohl, Leibniz Institute for Neurobiology, Brenneckestrasse 6, D-39118 Magdeburg, Germany.
e-mail: frank.ohl@ifn-magdeburg.de

†***Present address:***
Anton Ilango, Intramural Research Programme, National Institute on Drug Abuse, National Institutes of Health, 251 Bayview Blvd., Baltimore, MD 21224, USA.

Learning from punishment is a powerful means for behavioral adaptation with high relevance for various mechanisms of self-protection. Several studies have explored the contribution of released dopamine (DA) or responses of DA neurons on reward seeking using rewards such as food, water, and sex. Phasic DA signals evoked by rewards or conditioned reward predictors are well documented, as are modulations of these signals by such parameters as reward magnitude, probability, and deviation of actually occurring from expected rewards. Less attention has been paid to DA neuron firing and DA release in response to aversive stimuli, and the prediction and avoidance of punishment. In this review, we first focus on DA changes in response to aversive stimuli as measured by microdialysis and voltammetry followed by the change in electrophysiological signatures by aversive stimuli and fearful events. We subsequently focus on the role of DA and effect of DA manipulations on signaled avoidance learning, which consists of learning the significance of a warning cue through Pavlovian associations and the execution of an instrumental avoidance response. We present a coherent framework utilizing the data on microdialysis, voltammetry, electrophysiological recording, electrical brain stimulation, and behavioral analysis. We end by outlining current gaps in the literature and proposing future directions aimed at incorporating technical and conceptual progress to understand the involvement of reward circuit on punishment based decisions.

Keywords: dopamine, aversive stimuli, avoidance learning, intracranial self-stimulation, reward and punishment, dorsal vs. ventral striatum, lateral habenula, ventral tegmental area

INTRODUCTION

According to Skinner (1938), events that strengthen or increase the likelihood of preceding responses are called positive reinforcers, and events whose *removal* strengthens preceding responses are called negative reinforcers. Based on the affective attributes that determine the reinforcing nature of the unconditioned stimulus (US), these can also be classified as appetitive and aversive reinforcers, respectively (Konorski, 1967). Decades of research have documented phasic (short latency and short duration) dopamine (DA) signals evoked by appetitive reward or conditioned reward predictors and the modification of these signals by changes in reward value (e.g., magnitude, probability, and delay) or reward omission (Schultz et al., 1997). However, the DA neuron response to aversive reinforcers as a function of punishment prediction or avoidance has received far less research attention. Here we review convergent findings, obtained utilizing microdialysis, voltammetry, electrophysiological recording, and electrical brain stimulation, indicating that DA not only plays a role in coding aversive stimuli, but also serves essential functions for the formation of behavioral learning strategies aimed at the avoidance of aversive stimuli.

THE DOPAMINERGIC SYSTEM AND AVERSIVE STIMULI

The release of DA in the context of aversive stimuli has been extensively studied using microdialysis. For example, after stressful tail-stimulation extracellular DA levels were increased in the dorsal striatum, nucleus accumbens (NAc), and medial prefrontal cortex (PFC), suggesting involvement of nigrostriatal, mesolimbic, and mesocortical DA systems (Abercrombie et al., 1989; Boutelle et al., 1990; Pei et al., 1990). Moreover, regional differences in DA release have been demonstrated within the ventral striatum in response to aversive stimuli. Prolonged administration of footshock increased extracellular DA in the NAc shell but not core (Kalivas and Duffy, 1995). Furthermore, presentation of sensory stimuli preconditioned with footshock elevated DA levels in NAc (Young et al., 1993). Pretreatment with footshock over several days decreased cocaine-induced DA elevation in mPFC but increased DA in the NAc (Sorg and Kalivas, 1991, 1993; Ungless et al., 2010). In some studies, the DA response to aversive stimuli declined with repeated stress exposure (Imperato et al., 1992). Across studies, different experimental procedures (seconds vs. minutes; 1 min sampling period vs. 10 min sampling period; brief, novel aversive stimuli vs. repeated,

chronic aversive stimuli) have made it difficult to draw coherent conclusions.

While microdialysis is useful for directly measuring the localized concentration of DA within a brain region, its temporal sensitivity is limited, usually reflecting more tonic fluctuations in DA release averaged across intervals of 2–10 min. Fast scan cyclic voltammetry (FSCV), on the other hand, is an indirect measure of DA release interpreted from the electrical currents associated with the oxidation and reduction of DA but has high temporal resolution (on the order of 200 ms), which is capable of detecting phasic DA signals associated with a single learning trial. A recent study clarified the role of DA for processing appetitive and aversive reinforcers by measuring the phasic DA signal every 100 ms using FSCV in response to opposite hedonic taste stimuli (rewarding sucrose vs. aversive quinine). A strong DA increase in response to sucrose and DA decrease in response to quinine was found in the NAc and dorsolateral bed nucleus of the stria terminalis, suggesting suppression of DA in these two regions in response to aversive taste stimuli (Roitman et al., 2008; Park et al., 2012). However, a 3 s tail pinch with a soft rubber glove led to different results. A phasic DA increase was time-locked to the tail pinch in the dorsal striatum and NAc core, while an increase in the NAc shell was evident once the tail pinch was removed (Budygin et al., 2012). This suggests that the delivery and removal of aversive stimuli may trigger different DA responses in different projection regions. In addition to phasic DA transients in the NAc core time-locked to aversive physical stimuli, spontaneous DA transients have also been reported in response to aversive social confrontations, such as facing an aggressive resident followed by social defeat (Anstrom et al., 2009). The difference in phasic DA transients in the NAc shell and core in response to aversive events is consistent with a specific motivational role executed by different DA pathways (Salamone, 1994; Ikemoto and Panksepp, 1999; Salamone and Correa, 2002; Ikemoto, 2007).

On the level of single neuron activity, aversive stimuli have often been reported to inhibit phasic DA neuron firing in several species (Mirenowicz and Schultz, 1996; Schultz et al., 1997; See **Table 1**). However, some studies also reported increased phasic firing in response to an aversive conditioned stimulus (CS; e.g., Guarraci and Kapp, 1999). To gain further insights into such discrepant results, recent studies combined extracellular recording and unit identification by juxtacellular neurobiotin labeling (Ungless et al., 2004; Brischoux et al., 2009; Mileykovskiy and Morales, 2011). In response to aversive footshock, DA neurons from different components of the VTA (the dorsal parabrachial pigmented nucleus and the ventral paranigral nucleus) showed opposite modulation of firing, i.e., a reduction and an increase, respectively (Ungless et al., 2004; Brischoux et al., 2009). Valenti et al. (2011) further demonstrated that a single footshock inhibited most of the recorded DA neurons, but repeated footshock evoked different responses on DA neuronal population activity along the mediolateral direction, with predominant excitation on the medial side. Also, DA neurons which were inhibited by the CS signaling the arrival of aversive airpuff were located more medially in VTA and substantia nigra pars compacta (SNc) medial part as opposed to the lateral SNc DA neurons which were predominantly excited (Matsumoto and Hikosaka, 2009).

Mileykovskiy and Morales (2011) studied the response of VTA DA neurons to a CS paired with a tail shock US. Three types of responses from DA neurons were observed during the presentation of the aversive CS, some of which featured biphasic inhibition and excitation. But all of the response types featured an inhibitory pause in firing, the duration of which was correlated with the expression of fear.

Furthermore, inhibition of DA neuron (59%) firing evoked by fearful events such as free fall and shake was followed by offset-rebound excitation (phasic burst firing) upon their termination. Interestingly, the same DA neurons also displayed a reward prediction signal (modulated firing in response to a stimulus that is associated with later occurrence of a reward) when conditioned later with sugar pellet (Wang and Tsien, 2011). From the available evidence including recent optogenetic insights, our understanding of DA neuron response to appetitive and aversive stimuli has broadened. The vast majority of DA neurons appear excited by appetitive rewards and their predictors, and inhibited by aversive punishments and their predictors, as well as by reward omission (Tobler et al., 2003; Mileykovskiy and Morales, 2011; Wang and Tsien, 2011; Cohen et al., 2012).

DOPAMINE AND AVOIDANCE LEARNING

Avoidance learning is the process by which an individual learns a behavioral response to avoid aversive stimuli. An important feature of avoidance learning is that it is governed by *negative* reinforcement; that is, the *absence* of a stimulus motivates behavioral change. The mechanism for exactly how the absence of something can come to serve as a reinforcer has been a puzzle for learning theorists and the focus of much behavioral research. A popular theory accounting for this phenomenon is the two-process theory of avoidance (Dinsmoor, 2001), which states that an animal first learns a Pavlovian association that a CS, such as a tone, will be followed by an aversive US, such as a shock. This Pavlovian association then becomes the basis for operant learning, in that the CS becomes aversive in its own right and thus capable of motivating an operant response. The two-process theory proposes that the CS triggers a state of fear, which the animal then acts to reduce. Thus, fear reduction becomes the ultimate mechanism for negative reinforcement learning. However, here we outline evidence for an alternative mechanism: namely, the formation of an expectation of CS-US contingency is indeed a critical prerequisite, but the *violation of aversive expectation* when the animal performs the correct avoidance response directly activates the DA reward system. Thus, the ultimate mechanism for negative reinforcement learning is isomorphic with that of positive reinforcement learning, and it is dopaminergic.

Numerous studies have found specific effects of DA manipulations on avoidance learning. Beninger et al. (1989) found that low doses of DA antagonists impaired active avoidance responses without affecting motor behavior. Depletion of DA by 6-hydroxydopamine (6-OHDA) in the SNc (Cooper et al., 1973; Jackson et al., 1977; Salamone, 1994), NAc (McCullough et al., 1993), or PFC (Sokolowski et al., 1994) impaired the development and maintenance of active avoidance strategies, usually without affecting motor responses, including escape responses. Active avoidance behavior was also disrupted by alpha-methyl-p-tyrosine

Table 1 | Effect of aversive stimuli on mid brain DA neurons.

Citation	Methodological details	Aversive stimuli (US) or Aversive conditioned stimuli (CS)	Regions recorded	% Neuron response to aversive stimuli	% Neuron response to offset of aversive stimuli	Notes
Brown et al. (2009)	Extracellular recording in urethane anesthetized rats	Pinches of 15 s duration to the hindpaw Footshocks (0.5 Hz and 2 ms duration) at 5 mA intensity were delivered for 100 trials to the hind paw	SNc	18% inhibition to aversive stimuli 20% inhibition to aversive stimuli		Other recorded neurons did not respond to either pinch or electrical shock
Brischoux et al. (2009)	Extracellular recording and juxtacellular labeling in urethane anesthetized rats	Footshocks (20 Hz, 5 mA) and 4 s trains	VTA: dorsal parabrachial nucleus VTA: ventral paranigral nucleus	55% of labeled were inhibited		Others did not respond to shock Labeled DA neurons excited by footshock was reported
Cohen et al. (2012)	Extracellular recording (Tetrode) in DAT-Cre mice identification using optical stimulation of channelrhodopsin	Air puff to the face	VTA	All optogenetically identified DA neurons were inhibited for the aversive stimuli		<50% of optogenetically identified DA neurons were excited by reward predicting CS
Coizet et al. (2006)	Extracellular recording in urethane anesthetized rats	Footshock (0.5 Hz and 2 ms duration) at 5 mA intensity were delivered for 60 trials	SNc	72% inhibited 12% excited		
Coizet et al. (2010)	Extracellular recording in urethane anesthetized rats	Footshock (0.5 Hz and 2 ms duration) at 5 mA intensity were delivered for 100 trials	Dorsal SNc	<80% showed inhibition of firing		Inactivation of parabrachial nucleus abolished the nociceptive responses
Gao et al. (1990)	Extracellular recording in chloral hydrate anesthetized rats	Peripheral nociceptive stimulation (shock to the tail) of 1 ms and 15–20 mA	SNc	78% inhibited 15% excited		Stimulation of LHb increased the inhibitory responses
Gao et al. (1996)	Extracellular recording in chloral hydrate anesthetized rats	Peripheral nociceptive stimulation (shock to the tail) of 1 ms and 15–20 mA	SNc	<90% inhibited		LHb neurons showed opposite patterns
Mantz et al. (1989)	Extracellular recording and antidromic identification in ketamine anesthetized rats	Tail pinch for 10 s using forceps	Ventromedial mesencephalic tegmentum	mPFC projecting neurons: 65% excited and 25% inhibited NAc projecting neurons: 4% inhibited		

(Continued)

Table 1 | Continued

Citation	Methodological details	Aversive stimuli (US) or Aversive conditioned stimuli (CS)	Regions recorded	% Neuron response to aversive stimuli	% Neuron response to offset of aversive stimuli	Notes
Matsumoto and Hikosaka (2009)	Extracellular recording in behaving monkeys	Airpuff to the face	SNc and VTA	US 45% inhibited 10.6% excited 43.6% no response CS 23% inhibited 36.8 excited 39.8% no response		Similar responses for reward omission All, aversive CS inhibited neurons were excited for the reward conditioned CS Medial VTA and medial SNc neurons are predominantly inhibited by CS predicting air puff
Mirenowicz and Schultz (1996)	Extracellular recording in behaving monkeys	CS predicting air puff to the hand	SNc, VTA, and retrorubral field	31% inhibited <14% excited		<70% excited by the CS predicting juice reward
Mileykovskiy and Morales (2011)	Extracellular recording and juxtacellular labeling in awake rats	Fear conditioning: tone paired with tail shock (0.5–1.2 mA, 60 Hz, 1 s)	VTA	In fear conditioned rats Type 1 (60%): inhibited for onset of CS^+ Type 2 (20%): inhibited for onset and offset of CS^+ Type 3 (20%): biphasic excitatory or inhibitory responses followed by inhibitory pause		Correlations between inhibitory response and rats which discriminates the fear CS
Tsai et al. (1980)	Extracellular recording in urethane anesthetized rats	Single shock stimulation to sciatic nerve (square pulse of 4–10 V intensity and 0.3 ms duration Repeated footshocks (10–50 Hz)	SNc	<85% inhibited 6% excited Prolonged duration of inhibition	Rebound excitation Rebound excitation	
Ungless et al. (2004)	Extracellular recording and juxtacellular labeling in urethane anesthetized rats		VTA	83% are inhibited Others are non-responsive		
Wang and Tsien (2011)	Extracellular recording (Tetrode) in behaving mice	20 trials of fearful events (Free fall from 10 to 30 cm height and shake from 0.2–1 s) with 1–2 min inter-trial interval	VTA	Type 1 (59%): Suppression of firing in response to both events Type 2 (13%): Suppression of firing in response to both events	Type 1:offset-rebound excitation No effect	96% of the type 1 and type 2 DA neurons excited by the CS signaling reward

injections in NAc and rescued by DA injections (Bracs et al., 1982). The D2 antagonist sulpiride inhibited avoidance learning when injected into NAc, but not when injected into PFC, amygdala, or caudate putamen (Wadenberg et al., 1990). However, other studies found that D2 antagonist injections into NAc did not impair acquisition but did reduce conditioned responding during subsequent tests, whereas D1 antagonist injections into NAc impaired conditioned responding during both acquisition and subsequent testing (Boschen et al., 2011; Wietzikoski et al., 2012).

While it seems clear from these studies that some dopaminergic target regions play a DA-dependent role in avoidance learning, it is not yet fully transparent what this role is or which DA receptors are essential for it. Extensive work in our laboratory has addressed these questions using shuttle-box avoidance learning, either conditioned by a frequency-modulated (FM) tone or by a GO-NO GO discrimination paradigm using rising and falling FM tones, the processing of which depends on auditory cortex (Wetzel et al., 1998, 2008; Ohl et al., 1999). Microdialysis in auditory cortex and medial PFC showed that DA release in both structures reaches a peak during the first few trials of successful avoidance (Stark et al., 2001, 2008). The consequences of this initial DA release were clarified by subsequent reversal learning experiments, in which a consolidated GO response to two oppositely modulated FM tones was challenged by switching the requirement for one of the FM tones to a NO GO response (Stark et al., 2004). This resulted in an initial breakdown in avoidance responding to chance levels for all animals. However, some animals showed improvement in discrimination learning over subsequent days, and only these animals showed strong DA release in mPFC. This suggests an association between mPFC DA and the discovery of correct discrimination contingencies, and a facilitative or perhaps even causal role for DA in the formation of successful go vs. no go discrimination.

Neuronal activity in auditory cortex is known to be influenced by dopaminergic inputs (e.g., Bao et al., 2001) compatible with the anatomical connectivity from the VTA to the auditory cortex (e.g., Budinger et al., 2008). To investigate the role of specific DA receptors in auditory discrimination learning, a variety of DA agonists and antagonists were administered bilaterally to the auditory cortex both before and after training (Tischmeyer et al., 2003; Schicknick et al., 2008, 2012). The chief conclusion from these experiments was that only drugs affecting D1/D5 receptors are capable of depressing or enhancing discrimination learning. The most interesting effect was that the D1 agonist SKF 38393 injected before training did not influence acquisition during the training session but did lead to improved retrieval the next day. This effect was blocked by concurrent application of rapamycin, a specific inhibitor of the protein kinase mTOR implicated in the control of synaptic protein synthesis and relevant for memory consolidation in discriminative avoidance learning (Kraus et al., 2002). Taken together, these experiments suggest that DA release in auditory cortex is necessary for the FM tone conditioned avoidance response, and may enhance memory consolidation via a D1-receptor-mediated pathway.

While the administration of pharmacological agents is useful for elucidating specific receptor pathways, this approach is limited in that it alters tonic neuromodulation over a prolonged period of time without informing, and perhaps even interfering with, the role of dynamic neuromodulation, i.e., the up-and-down fluctuations in neuromodulators over very short time scales. Based on the evidence outlined in the previous sections, such phasic changes in the DA signal may be especially relevant to incentivized learning. Specifically, DA neurons are known to respond to the omission of an expected appetitive stimulus with a momentary cessation in firing. We theorized that DA neurons would greet the omission of an expected aversive stimulus in a symmetrical manner, namely, with a transient burst in firing. Signaled active avoidance learning inherently leads to such a negative expectation (e.g., shock will follow tone) as well as its subsequent violation (e.g., shock does not follow tone if hurdle is promptly crossed). Could DA involvement in avoidance learning be specific to the trials when the expectation of shock is violated, that is, when the animal first performs a successful avoidance response? Could a pronounced DA increase at this critical moment be responsible for reinforcing the avoidance response?

If so, a transient disruption of DA transmission following the initial trials of successful avoidance responding (when the animal is pleasantly surprised by the absence of shock) should disrupt learning. On the other hand, an equivalent manipulation following later trials after the avoidance response is well learned (when the animal fully expects that its behavior will lead to the absence of shock) should have no effect. Electrical stimulation of the lateral habenula (LHb), which results in transient, widespread inhibition of DA neurons in rodents and primates (Christoph et al., 1986; Ji and Shepard, 2007; Matsumoto and Hikosaka, 2007), was used to test this hypothesis (Shumake et al., 2010). Specifically, we implanted the LHb with a stimulation electrode and delivered brief electrical stimulation whenever the animal performed a correct avoidance response, i.e., when the initial avoidance of foot shock was hypothesized to trigger an intrinsic reward signal. As predicted, LHb stimulation initiated early in training impaired learning, but LHb stimulation initiated late in training had no effect (Shumake et al., 2010; **Figure 1**). These findings suggest a vital role for phasic DA signaling in the successful acquisition of active avoidance behavior. What is not yet clear is whether the presumed phasic increases in DA add up to the tonic increases in forebrain DA levels previously observed (Stark et al., 1999, 2000; Giorgi et al., 2003), or whether phasic and tonic DA signals convey differential information in the context of avoidance learning.

BRAIN STIMULATION REWARD AND AVOIDANCE LEARNING

Since James Olds discovered intracranial self-stimulation (ICSS; Olds and Milner, 1954; Olds, 1958), several ICSS-supporting regions have been characterized. The majority of these regions lie along DA projections, such that robust ICSS can be evoked from the VTA, substantia nigra, and lateral hypothalamus. Moreover, extracellular DA elevation is necessary to maintain ICSS (Fibiger et al., 1987; Fiorino et al., 1993; Owesson-White et al., 2008). Over the years, the effects of brain stimulation reward (BSR) were studied in learning and memory experiments, and it was found that BSR applied as experimenter-delivered stimulation or self-stimulation by the animal facilitated avoidance learning (Mondadori et al., 1976; Huston et al., 1977; Destrade and Jaffard, 1978; Segura-Torres et al., 1988, 1991, 2010; Huston and Oitzl, 1989; Aldavert-Vera et al., 1997; Ruiz-Medina et al., 2008). These

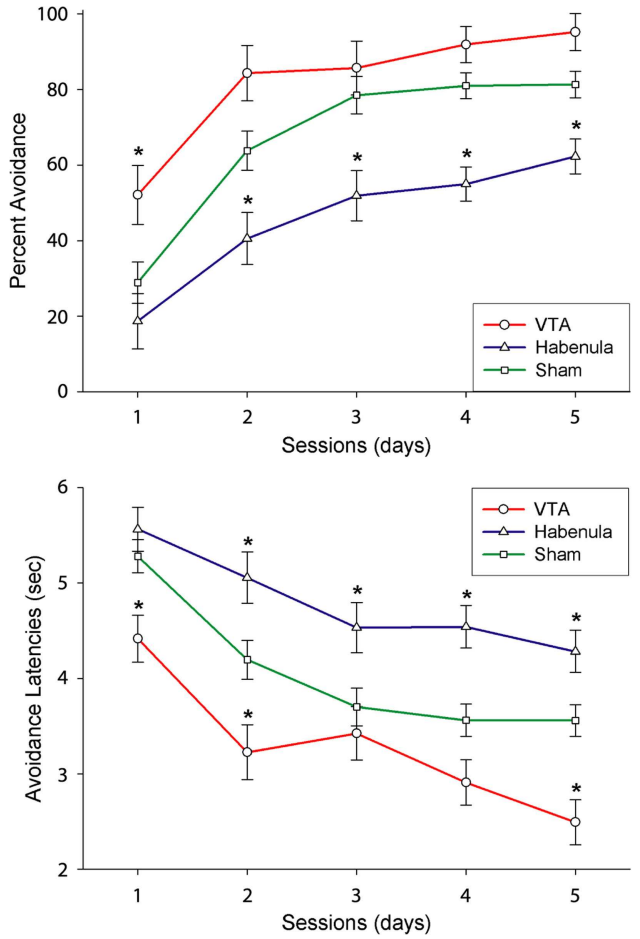

FIGURE 1 | Effect of VTA vs. LHb stimulation on the acquisition of avoidance. Upper and lower panels indicate the Mean and SEs of successful avoidance trials and avoidance latency. Asterisks indicate significant differences between stimulated vs. control group (Modified from "Shumake et al., 2010").

results show that BSR given before or after training led to improvement of avoidance learning by improving the learning efficiency. However, correct avoidance responding is reinforced not only by terminating the aversive warning signal, i.e., relief from fear, but also by producing a safety signal, i.e., response-generated feedback stimuli signaling safety (Cicala and Owen, 1976; Dinsmoor, 1977; Masterson et al., 1978). Concerning the aversive component, the potential for enhancing the strength of reinforcement, e.g., by increasing shock intensity, is rather limited. Concerning the appetitive component, however, it is possible to enhance the magnitude of reinforcement by using additional feedback stimuli, e.g., sensory cues contingent to avoidance (Morris, 1975; Cicala and Owen, 1976), access to a safe place (Modaresi, 1975; Baron et al., 1977), or handling during the inter-trial interval (Wahlsten and Sharp, 1969).

These data support the view that any stimuli negatively correlated with shock, whether exteroceptive (presented by the experimenter) or interoceptive (presented by the subject's own behavior), are inherently rewarding (Dinsmoor, 2001). Compatible with this idea, recent MRI studies in humans have suggested that activity in the medial orbitofrontal cortex, a reinforcement evaluating area, reflects an intrinsic reward signal that serves to reinforce avoidance behavior (Kim et al., 2006). Thus, we can assume that in aversively motivated learning, avoidance learning responses come under the control of positive incentives. Earlier investigations on appetitive-aversive interactions have shown that appetitive training appears to facilitate subsequent aversive conditioning (Dickinson, 1976; Dickinson and Pearce, 1977) and that operant behavior is enhanced by using concurrent schedules of positive and negative reinforcement (Kelleher and Cook, 1959; Olds and Olds, 1962). Moreover, a few studies reported the facilitation of discrete-trial avoidance (Stein, 1965; Castro-Alamancos and Borrell, 1992) and Sidman avoidance (in which shock is not signaled but rather occurs at fixed intervals unless the animal performs the operant response; Margules and Stein, 1968; Carder, 1970) by *non-contingent* rewarding brain stimulation, an effect resembling the action of stimulant drugs like amphetamine on self-stimulation and avoidance performance.

These results support the idea that the brain reward system facilitates operant behavior, whether positively or negatively reinforced. Not tested, however, was the effect of BSR given *contingently* to a correct response, i.e., exactly during the time-point when the response-generated safety signal occurs. Thus, in our studies we used the shuttle-box two-way avoidance paradigm to provide a way to combine BSR with footshock negative reinforcement to drive the same learned operant behavior. We found that this reinforcer combination potentiated the speed of acquisition, led to superior (nearly 100% correct) performance and delayed extinction, as compared to either reinforcer alone (Ilango et al., 2010, 2011; Shumake et al., 2010). These findings demonstrate that adding intrinsic reward (by stimulating dopaminergic structures) to the relief from punishment results in maximum avoidance performance, supporting the view that brain reward circuits serve as a common neural substrate for both appetitively and aversively motivated behavior.

PERSPECTIVES

In conclusion, several lines of evidence strongly argue in favor of the involvement of reward circuitry for the processing of aversive stimuli, especially to encode their predictors and to form an instrumental strategy to avoid them (e.g., Brischoux et al., 2009; Matsumoto and Hikosaka, 2009; Bromberg-Martin et al., 2010; Ilango et al., 2010, 2011; Budygin et al., 2012). Specifically, the neurotransmitter DA is involved in neuronal and behavioral responses to cues predicting reward (approach) or punishment (avoidance), both of which are vital for adaptive behavior. Electrophysiological signatures obtained from VTA DA neurons have begun to reveal their convergent encoding strategy for mediating both appetitive and aversive learning (Kim et al., 2012). Furthermore, VTA BSR can be integrated into avoidance learning tasks to investigate the nature of reinforcer interaction, and to understand the similarity between affective states associated with absence of predicted appetitive stimuli (frustration) and predicted aversive stimuli (fear) vs. absence of predicted aversive stimuli (relief) and

predicted appetitive stimuli (hope; Seymour et al., 2007; Ilango et al., 2010).

Further progress in understanding the neuronal basis of affective behaviors will rely on both technical and conceptual progress. On the technical side, optogenetic approaches will allow triggering temporally precise events in specific cell types. For example, driving DA neurons in VTA by channelrhodopsin has already been demonstrated to support vigorous intracranial self-stimulation and place preference (Tsai et al., 2009; Witten et al., 2011). Such approaches could be extended to clarify the respective roles of several cell populations in different behaviors.

On the conceptual side, behavioral paradigms that allow the assessment of DA-related neuronal signatures in flexible scenarios will be important. For example, deeper insight into the role of DA with respect to the dissociation between (1) the association of specific behavioral meaning to stimuli and (2) the organization of appropriate behaviors can be expected from comparison of Pavlovian and instrumental paradigms. Also, discriminative avoidance learning tasks can be used to investigate how the same DA neuron responds to a CS+ in a hit vs. a miss trial or to a CS- in false-alarm vs. a correct-rejection trial, thereby allowing assessment of which factors govern the recruitment of excitatory and inhibitory contributions to neuronal and behavioral responses.

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Encoding of aversion by dopamine and the nucleus accumbens

James E. McCutcheon, Stephanie R. Ebner, Amy L. Loriaux and Mitchell F. Roitman*

Department of Psychology, University of Illinois at Chicago, Chicago, IL, USA

Edited by:
Philippe N. Tobler, University of Zurich, Switzerland

Reviewed by:
A. David Redish, University of Minnesota, USA
Mark Ungless, Imperial College London, UK

****Correspondence:***
Mitchell F. Roitman, Department of Psychology, University of Illinois at Chicago, 1007 W Harrison Street, Chicago, IL 60607, USA.
e-mail: mroitman@uic.edu

Adaptive motivated behavior requires rapid discrimination between beneficial and harmful stimuli. Such discrimination leads to the generation of either an approach or rejection response, as appropriate, and enables organisms to maximize reward and minimize punishment. Classically, the nucleus accumbens (NAc) and the dopamine projection to it are considered an integral part of the brain's reward circuit, i.e., they direct approach and consumption behaviors and underlie positive reinforcement. This reward-centered framing ignores important evidence about the role of this system in encoding aversive events. One reason for bias toward reward is the difficulty in designing experiments in which animals repeatedly experience punishments; another is the challenge in dissociating the response to an aversive stimulus itself from the reward/relief experienced when an aversive stimulus is terminated. Here, we review studies that employ techniques with sufficient time resolution to measure responses in ventral tegmental area and NAc to aversive stimuli as they are delivered. We also present novel findings showing that the same stimulus – intra-oral infusion of sucrose – has differing effects on NAc shell dopamine release depending on the prior experience. Here, for some rats, sucrose was rendered aversive by explicitly pairing it with malaise in a conditioned taste aversion paradigm. Thereafter, sucrose infusions led to a suppression of dopamine with a similar magnitude and time course to intra-oral infusions of a bitter quinine solution. The results are discussed in the context of regional differences in dopamine signaling and the implications of a pause in phasic dopamine release within the NAc shell. Together with our data, the emerging literature suggests an important role for differential phasic dopamine signaling in aversion vs. reward.

Keywords: voltammetry, electrophysiology, conditioned taste aversion, taste reactivity, reward, ventral tegmental area

INTRODUCTION

Since Olds and Milner's (1954) seminal observation that animals will self-administer current to regions of their own brain, behavioral neuroscientists have been captivated by the prospect of brain "reward circuits." During the intervening years, a strong case has been made for the nucleus accumbens (NAc) and NAc-projecting dopamine neurons in the ventral tegmental area (VTA) as being critical cogs in brain reward circuitry. Although the precise relationship between dopamine and reward is still under debate (Berridge and Robinson, 1998; Wise, 2004; Salamone, 2007; Redgrave et al., 2008; Beeler et al., 2012), it is clear that NAc and dopamine participate in processing rewarding stimuli and the generation of reward-directed actions (Schultz, 2000; Kelley et al., 2005; Fields et al., 2007; Kenny, 2011). With respect to dopamine neurotransmission, there is robust agreement using a variety of tools, that the majority of dopamine neurons increase their firing rate and dopamine concentration increases in NAc in response to unpredicted primary rewards or cues that reliably predict rewards (Schultz, 1998; Roitman et al., 2004; Matsumoto and Hikosaka, 2009; Cohen et al., 2012; McCutcheon et al., 2012). However, there has been comparatively little attention paid to dopamine responses to aversive stimuli. Although it is increasingly recognized that the NAc and dopamine process aversive stimuli, the manner in which such stimuli are encoded by this system remains unclear.

Our behavior is potently modified by both beneficial and harmful outcomes. Inappropriate affective responses are hallmarks of many psychiatric disorders including depression, bipolar, and other mood disorders. For example, in animal models drug-addicted rats will continue to respond for drug even if they must simultaneously endure a foot shock that would normally be considered aversive (Deroche-Gamonet et al., 2004; Vanderschuren and Everitt, 2004). These findings are proposed to be analogous to the insensitivity of human drug addicts to the costs associated with continued drug seeking and taking. While there has been a traditional focus on dopamine and the NAc in behavior associated with beneficial outcomes, it is imperative to gain a further understanding of the nature of NAc-dopamine signaling in aversion and to determine whether these components play as strong a role in rejection responses and avoidance learning as they do in appetitive responses and approach learning.

DEFINITION OF AVERSION

Like reward (Berridge and Robinson, 2003), aversion is a multidimensional construct. Most aversive stimuli are intensely disliked and will motivate avoidance. However, it is important to note that

dislike and avoidance are not synonymous. As such, dislike is a hedonic evaluation and is common to all aversive stimuli (Kravitz and Kreitzer, 2012). In other words, to be considered aversive, experience of the stimulus should induce a negative hedonic state. However, this definition is problematic as monitoring an animal's hedonic state is difficult, and in some cases impossible. When using taste stimuli the well-established method of taste reactivity (Grill and Norgren, 1978) has been used to quantify hedonic evaluation in human and non-human subjects alike (Berridge, 2000; Steiner et al., 2001). In contrast, for other sensory modalities such an evaluation is more difficult to quantify. Emission of ultrasonic vocalizations (increase in 22 kHz or decrease in 50 kHz) is thought to be related to hedonia (Knutson et al., 2002) but the utility of this method in assessing hedonic state over a wide range of situations has not been comprehensively validated. Thus, due to the difficulty in assessing hedonic state, in many studies of aversive stimuli, avoidance is used as a proxy for aversion.

When considering the concept of avoidance there are important differences between the production of a behavior that avoids an aversive event (negative reinforcement) and suppression of a behavior that would lead to an aversive event (absence of punishment). Additionally, omission of an expected reward, disappointment, and subsequent extinction of behavior, can also be dissociated from aversion as defined here, and these events may invoke a different set of learning mechanisms (Redish et al., 2007). These distinctions between psychological constructs (hedonic evaluation, reinforcement, punishment, and disappointment) are important as they are likely sub-served by distinct processes at both the systems and cellular/molecular level (Kravitz and Kreitzer, 2012). Indeed, although there is often good overlap between dislike and avoidance there are instances during which these become dissociated. In summary, aversion and avoidance should not be equated and care should be taken when extrapolating the aversive nature of a particular stimulus from its ability to generate or suppress behavior.

Importantly, modulatory factors including motivational state and learning from previous experience can also have powerful effects on the hedonic evaluation of a stimulus. A striking example of motivational state affecting stimulus evaluation is that of salt appetite. Normally, hypertonic sodium chloride solutions are perceived as aversive and unpalatable. In times of need, however, such as following sodium depletion, these solutions become rewarding rather than aversive (Berridge et al., 1984; Tindell et al., 2006); this shift in hedonic valence is accompanied by changes in neuronal activity evoked by hypertonic sodium chloride solutions in NAc (Loriaux et al., 2011) and ventral pallidum (Tindell et al., 2006). Likewise, history with a hedonic stimulus can alter hedonic reactions to it when next encountered. Sweet solutions normally evoke positive hedonic responses. However, if the taste of a sweet solution is paired with malaise, a conditioned taste aversion (CTA) can develop and the same solution is now met with negative hedonic reactions. This shift in hedonic valence is accompanied by changes in neuronal activity evoked by sweet solutions in NAc (Roitman et al., 2010) and basolateral nucleus of the amygdala (Kim et al., 2010). The ability of motivational state and learning to radically alter the nature of a stimulus should make us wary of assuming the hedonic value of a stimulus. This is particularly relevant to studies performed in anesthetized animals. By its very nature, the anesthetic agent is likely to have dampened the negative hedonic state and thus removed the contribution of the neural circuits that may be of most importance for the aversive experience. In this light, the study of "aversive" stimuli under anesthesia may be fundamentally flawed and should be interpreted with caution. This topic will be returned to in the following paragraphs.

Finally, the temporal nature of aversion can vary and states such as stress and fear may consist of negative hedonic states which persist for long periods. For our purposes, we will focus on discrete stimuli that occur on a timescale of seconds. Specifically, with respect to stress, although many of the aversive experiences we will discuss have also been described as acute stressors and when used chronically produce stress-like symptoms (e.g., dysregulation of hypothalamic-pituitary axis and associated behavioral phenotypes), we will not discuss these data. Instead, we refer the interested reader to excellent reviews on stress, dopamine, and NAc (Marinelli et al., 2006; Nestler and Carlezon, 2006; Koob, 2008).

Here, we focus on how aversion may be encoded by mesolimbic dopamine and the implications for NAc processing. A possible confound when studying the encoding of aversion is that there is relief when aversion is terminated – which is likely to be rewarding. In human subjects, offset of a painful stimulus increases blood flow to the NAc, indicating that this region is activated by relief (Baliki et al., 2010). Thus, we will focus on electrophysiological and electrochemical recordings with sufficient time resolution to correlate changes in activity with the onset and duration of aversive events. We review data and present novel findings that unequivocally demonstrate that classical brain reward circuitry is also exquisitely sensitive to aversive stimuli.

MODULATION OF DOPAMINE CELL FIRING AND RELEASE BY REWARD

Dopamine neurons within the substantia nigra pars compacta (SNc) and VTA project to dorsal and ventral striatum, respectively. In the vast majority of studies made in primate and rodent subjects, during reward-related stimuli – e.g., presentation of primary reward, reward-predictive cues, and during reward-directed actions (Schultz, 1998; Joshua et al., 2008; Matsumoto and Hikosaka, 2009; Cohen et al., 2012) – these neurons show a fairly homogenous response. That is, the majority of dopamine neurons respond to such stimuli and they do so uniformly by exhibiting brief, high frequency increases in firing rate. This pattern of neural activity is likely to cause transient increases in dopamine concentration within the striatum – which has been empirically demonstrated (Garris et al., 1997; Phillips et al., 2003; Venton et al., 2003; Roitman et al., 2004; Sombers et al., 2009; Owesson-White et al., 2012). Indeed, using the electrochemical technique of fast-scan cyclic voltammetry, which can detect fluctuations in dopamine concentration on a timescale similar to electrophysiological changes in dopamine neural activity, it has been repeatedly demonstrated that primary reward and reward-predictive stimuli evoke brief increases in dopamine concentration (Robinson et al., 2002; Phillips et al., 2003; Roitman et al., 2004; Owesson-White et al., 2008; Stuber et al., 2008; Brown et al., 2011; McCutcheon et al., 2012). Voltammetry has excellent face validity for capturing fluctuations in dopamine concentration that result from transient

activations and suppressions of dopamine cell firing (Sombers et al., 2009; Owesson-White et al., 2012). Thus, combining the literature in which either electrophysiological recordings from dopamine neurons or electrochemical recordings of dopamine release were made, the population response of midbrain dopamine neurons to rewarding stimuli appears to be a transient increase in activity.

MODULATION OF DOPAMINE CELL FIRING BY PRIMARY AVERSIVE STIMULI

Relative to the reward literature, there are far fewer examinations of the dopamine neuron response to aversive events. In the studies that have been conducted with aversive stimuli, outcomes are much less uniform than seen when reward-related stimuli are used. As such, aversive events are commonly shown to have both excitatory and inhibitory effects on the firing of midbrain dopamine neurons. These studies are reviewed in **Table 1**. A clear conclusion on the encoding of aversive stimuli by the firing rate of dopamine neurons is limited by several factors. First, identification of neurons within VTA and SNc as dopaminergic based on electrophysiological characteristics remains somewhat controversial (Ungless and Grace, 2012). Second, responses to aversive stimuli have been characterized in either anesthetized or awake and behaving subjects. As discussed earlier, anesthesia may suppress components of the circuit that, when awake would contribute to the generation of a very different dopamine response (Koulchitsky et al., 2012). Third, a wide variety of aversive stimuli have been used to compare with reward-responses. Aversive stimuli used to date include, shock, air puff, foot or tail pinch, and aversive taste stimuli. These stimuli are transduced along very different sensory pathways. They also differ in their intensities and have been characterized from mildly aversive to noxious/painful. Finally, many studies use cues that have been associated with the occurrence of an aversive event and the cue itself comes to elicits a behavior that protects the animal against the aversive stimulus, e.g., an eye blink. Thus, the heterogeneity in dopamine responses to aversive stimuli to date may represent real heterogeneity among different pools of dopamine neurons (Brischoux et al., 2009; Matsumoto and Hikosaka, 2009; Lammel et al., 2011) but may also reflect the heterogeneity of investigative approaches.

MODULATION OF DOPAMINE RELEASE BY AVERSION

Fluctuations in dopamine concentration in dopamine terminal regions overcome some of the limitations of recording neural activity in the ventral midbrain. There is no controversy surrounding the identity of the compound studied when microdialysis or fast-scan cyclic voltammetry are used. Microdialysis, though, lacks the sampling resolution required to resolve changes in dopamine evoked by discrete aversive stimuli. Only a handful of studies have employed fast-scan cyclic voltammetry to measure fluctuations in dopamine concentration evoked by aversion (**Table 2**) (Roitman et al., 2008; Anstrom et al., 2009; Wheeler et al., 2011; Budygin et al., 2012) and are subject to the issues identified earlier: specifically, stimuli that are not temporally discrete, stimuli that are transduced along different sensory pathways than rewarding stimuli, and studies that are performed in anesthetized animals. Recently, we and others have measured dopamine fluctuations during intra-oral delivery of rewarding and aversive taste stimuli. Intra-oral delivery, when paired with fast-scan cyclic voltammetry, offers several advantages. First, primary taste stimuli can be selected to evoke reliable and stereotypical appetitive and aversive responses which can be quantified using taste reactivity (Grill and Norgren, 1978; Peciña and Berridge, 2000). Second, rewarding and aversive stimuli are transduced via similar sensory machinery – that is, the taste system. Third, the animal's exposure to a stimulus can be tightly controlled, which is particularly important when studying stimuli, e.g., a bitter solution, that an animal would actively avoid. Thus, in conjunction with fast-scan cyclic voltammetry, dopamine concentration fluctuations on a timescale commensurate with the subject's sensory experience can be measured. Using different stimuli, we have shown that an appetitive sucrose solution increases while an aversive quinine solution suppresses phasic dopamine concentration fluctuations in the NAc shell subregion (Roitman et al., 2008). Recordings were made in a region identified as a "hedonic hotspot" (Peciña and Berridge, 2005). These effects were replicated and extended to taste solutions that are used as conditioned stimuli. When one flavored sweet solution predicted the delayed opportunity to self-administer cocaine, it acquired aversive properties (Wheeler et al., 2011). This solution also suppressed phasic fluctuations in NAc shell dopamine concentration whereas a differently flavored sweet solution increased NAc shell dopamine. Thus, rewarding taste stimuli increase and aversive taste stimuli suppress phasic fluctuations in NAc shell dopamine concentration – suggesting that reward and aversion both evoke changes in phasic dopamine signaling but in opposite directions. However, in both studies, different taste solutions were compared. Perhaps the most rigorous test of differential encoding of reward and aversion by phasic dopamine would be to use the same stimulus but in each case to change the animal's hedonic evaluation of that stimulus. We accomplished this using a CTA paradigm. Here, we measured phasic dopamine signaling in the NAc shell during intra-oral delivery of a sucrose solution. However, for half of the rats (Paired), this sucrose solution had been previously paired with a malaise-inducing injection of lithium chloride in a CTA paradigm. This classical conditioning procedure renders the sucrose solution aversive (Roitman et al., 2010) – which we quantified using taste reactivity. As such, responses to an identical taste stimulus can be compared between rats that have undergone the CTA procedure and those that have not (Unpaired).

SUCROSE DIFFERENTIALLY MODULATES PHASIC DOPAMINE CONCENTRATION FLUCTUATIONS DEPENDING ON ITS HEDONIC VALUE

Male Sprague-Dawley rats (Charles River; $n = 15$) were used. Two cohorts were dedicated to the CTA experiment and were divided into Paired ($n = 5$) vs. Unpaired ($n = 5$) groups. A third group received intra-oral infusions of quinine as a comparison ($n = 5$). All rats were singly housed under standard housing conditions. Food and water were available *ad libitum* throughout the experiment. Surgical procedures were identical to Roitman et al. (2008). Briefly, under ketamine/xylazine anesthesia, rats were surgically implanted with intra-oral catheters, a guide cannula directed at the NAc shell, an Ag/AgCl reference wire in the contralateral cortex, and a bipolar stimulating electrode in the midbrain. After

Table 1 | Neuronal responses of midbrain dopamine neurons to aversive stimuli.

Reference	Species	Awake?	Aversive event	Region	Cell ID	Outcome	Comments
Chiodo et al. (1980)	Rat*	No	Air puff to snout	SNc	EP, Ph	49% Increase, 51% decrease	Inhibited cells have a longer waveform; similar results seen in VTA (unpubl.)
Maeda and Mogenson (1982)	Rat*	No	Foot pinch	SNc, VTA	None	28% Increase, 55% decrease	Divided cells into type I and type II; results shown are combined
Kiyatkin (1988)	Rat	Yes†	Tail prick	VTA	EP	67% Increase, 26% decrease	
Schultz and Romo (1987)	Monkey	No	Pinch to face, hand, foot, and tail	SNc	EP, AD, Ph	17% Increase, 51% decrease	
Mantz et al. (1989)	Rat	No	Tail pinch	VTA	EP, AD	0% Increase (MA), 65% increase (MC), 11% decrease(MA), 25% decrease (MC)	Ketamine used for anesthesia
Gao et al. (1990)	Rat*	No	Tail shock	SNc	EP, AD	15% Increase, 78% decrease	
Mirenowicz and Schultz (1996)	Monkey	Yes	Air puff to hand, hypertonic saline, aversive cues	SNc, VTA	EP	14% Increase (US), 3–14% increase (CS), 31% decrease (CS)	Avoidance paradigm – aversive event rarely encountered; potential mediolateral gradient
Guarraci and Kapp (1999)	Rabbit	Yes	Aversive cues (predicting shock to pinna)	VTA	EP	29% Increase, 14% decrease	
Ungless et al. (2004)	Rat	No	Foot pinch	VTA	IHC, EP	0% Increase, 83% decrease	
Coizet et al. (2006)	Rat*	No	Foot pinch and shock	SNc	EP	12% Increase, 72% decrease	
Joshua et al. (2008)	Monkey	Yes	Air puff to eye, aversive cue	SNc	EP, Ph	Increase across population to CS and US	
Brischoux et al. (2009)	Rat	No	Electric shock to paw	VTA	IHC, EP	36% Increase, 36% decrease	Dorsal-ventral segregation of responses
Brown et al. (2009)	Rat	No	Pinch or electric shock to paw	SNc	IHC	5% Increase (pinch), 18% decrease (pinch), 0% increase (shock), 20% decrease (shock)	
Matsumoto and Hikosaka (2009)	Monkey	Yes	Air puff, aversive cue	SNc, VTA	EP	37% Increase (CS), 23% decrease (CS), 11% increase (US), 46% decrease (US)	Dorsolateral–ventromedial segregation of CS and US responses
Mileykovskiy and Morales (2011)	Rat	Yes	Aversive cue (predicting tail shock)	VTA	IHC	20% Increase/decrease, 60% decrease/increase, 20% decrease/decrease	Biphasic responses of cells to onset and offset of CS
Wang and Tsien (2011)	Mouse	Yes	Free fall, shake, aversive cues	VTA	EP	25% Increase (US), 72% decrease (US), 50% increase (CS), 50% decrease (CS)	Many cells show rebound excitation at offset of aversive stimulus
Zweifel et al. (2011)	Mouse	Yes	Foot pinch	VTA	Ph, EP	35% Increase, 35% decrease	Similar results in quinpirole-insensitive neurons
Cohen et al. (2012)	Mouse	Yes	Air puff to face	VTA	Opto	12% Increase, 24% decrease	Excitations in 93% of GABA neurons

*Percentages are of total "identified" population. *Female; † head-restrained; SNc, substantia nigra pars compacta; VTA, ventral tegmental area; EP, electrophysiological; Ph, pharmacological; AD, antidromic stimulation; IHC, immunohistochemical; Opto, optogenetic; CS, conditioned stimulus; US, unconditioned stimulus; MA, mesoaccumbal; MC, mesocortical.*

Table 2 | Phasic dopamine responses to aversive stimuli.

Reference	Species	Awake?	Aversive event	Region	Outcome	Comments
Kiyatkin (1995)	Rat	Yes	Tail pinch	NAc	Increase	Slow time course, e.g., over minutes
Roitman et al. (2008)	Rat	Yes	Quinine infusion	NAc shell	Decrease to stimulus	
Anstrom et al. (2009)	Rat	Yes	Social defeat	NAc core	Increase in transients	
Wheeler et al. (2011)	Rat	Yes	Infusion of cocaine-paired saccharin solution	NAc shell	Decrease to stimulus	
Budygin et al. (2012)	Rat	No	Tail pinch	NAc core and shell dStri	Increase to stimulus	Greater in NAc than in dStri; slow onset in NAc shell
Park et al. (2012)	Rat	Yes	Quinine	dlBNST	Decrease to stimulus	

NAc, nucleus accumbens; dStri, dorsal striatum; dlBNST, dorsolateral bed nucleus of stria terminalis.

recovery from surgery, Paired and Unpaired rats underwent conditioning. Paired rats received 30 intra-oral sucrose infusions (0.3 M; 200 μL; 4 s; 30–90 s inter infusion interval) on Days 1 and 3 followed immediately by an injection of LiCl (0.15 M; 20 mL/kg; i.p.). On Days 2 and 4, this cohort received saline injections (0.9%; 20 mL/kg; i.p.) in their home cages. For Unpaired rats, the procedure was identical except the injection order was reversed so that intra-oral sucrose infusions were followed by saline injections on Days 1 and 3 and LiCl injections were delivered in home cage on Days 2 and 4. Thus, both groups had the same number of sucrose infusions, LiCl, and saline injections, however, Paired rats had sucrose explicitly paired with LiCl whereas Unpaired rats did not. Quinine rats underwent no conditioning sessions. Next, all rats had a carbon fiber electrode lowered into NAc shell and dopamine release was recorded using fast-scan cyclic voltammetry while rats received sucrose (CTA rats) or quinine infusions, under the same schedule as in training. Dopamine concentration was extracted from current-voltage plots using established methods (Heien et al., 2004; Keithley et al., 2010). For CTA rats, 1–5 days after the recording session, taste reactivity to intra-oral sucrose infusions was video taped and movies were scored for positive (tongue protrusions, lateral tongue protrusions), and negative (gapes, forelimb flails, chin rubs) responses consistent with previous reports (Peciña and Berridge, 2000). At the end of the experiment, in all rats, the recording site was lesioned, rats were transcardially perfused and brains were sectioned for *post hoc* histological confirmation of recording placement.

We (Roitman et al., 2008; Owesson-White et al., 2012) and others (Wightman et al., 2007; Sombers et al., 2009) have reported that phasic dopamine release events occur "spontaneously" without being evoked by any overt stimuli. Here, recordings in the NAc shell captured "spontaneous" dopamine release events (**Figures 1A–C**). Indeed, as seen in the representative trials in **Figure 1**, dopamine release events were observed in the seconds prior to intra-oral infusions in examples from all three groups. Intra-oral infusions differentially modulated the frequency with which these events occurred. While quinine delivered to naïve rats (**Figure 1A**) and sucrose delivered to Paired rats (**Figure 1B**) suppressed dopamine release events, sucrose delivered to Unpaired rats (**Figure 1C**) increased their frequency.

As dopamine release events occurred during the pre-infusion epoch, averaging across trials led to a baseline dopamine concentration from which quinine caused a significant decrease ($p = 0.032$ for pre- vs. infusion epoch; **Figure 2A**). In CTA rats, sucrose infusions had opposing effects on averaged dopamine concentration relative to the pre-infusion epoch dependent on the conditioning history of the animal (Epoch × CTA interaction, $F_{1,9} = 7.89$, $p = 0.023$; **Figure 2B**). In Paired rats, which had CTA induced by pairing sucrose with illness, infusions of sucrose caused a significant suppression of dopamine (*post hoc* Tukey's test, $p = 0.007$; **Figure 2B**, red trace) similar to what we observed with quinine infusions. In contrast, in Unpaired rats we saw a small increase in average dopamine concentration that was not statistically significant (**Figure 2B**, blue trace). While in the past we have shown that intra-oral sucrose infusions increase average dopamine concentration in the NAc shell (Roitman et al., 2008), the increase was evoked in naïve rats. Using microdialysis, Di Chiara and colleagues have shown that increases in NAc shell dopamine to novel food reward dissipate with repeated exposure (Bassareo and Di Chiara, 1999). Thus, the weak increase observed in response to sucrose in Unpaired rats may be due to their familiarity with the rewarding sucrose solution.

Conditioned taste aversion rats received a session of sucrose infusions and their orofacial responses were analyzed. In Paired rats, sucrose infusions evoked predominantly negative orofacial movements whilst sucrose evoked predominantly positive orofacial movements in Unpaired rats (**Figure 3**). These differences were confirmed using Mann–Whitney *U*-tests: paired rats had both higher negative scores and lower positive scores than Unpaired rats ($ps < 0.05$). The data clearly demonstrate that while both groups of rats had equal exposure to sucrose and LiCl, a CTA was established only in Paired rats. Importantly, taken together with dopamine concentration fluctuations, the data establish that in this paradigm, the NAc shell dopamine response matches the hedonic value of the stimulus and, when aversive, the taste stimulus suppresses phasic dopamine signaling.

Electrophysiological recordings from dopamine neurons suggest a heterogeneous response to aversive stimuli – with some studies supporting mostly inhibitory responses (Mirenowicz and Schultz, 1996; Ungless et al., 2004; Cohen et al., 2012) and others

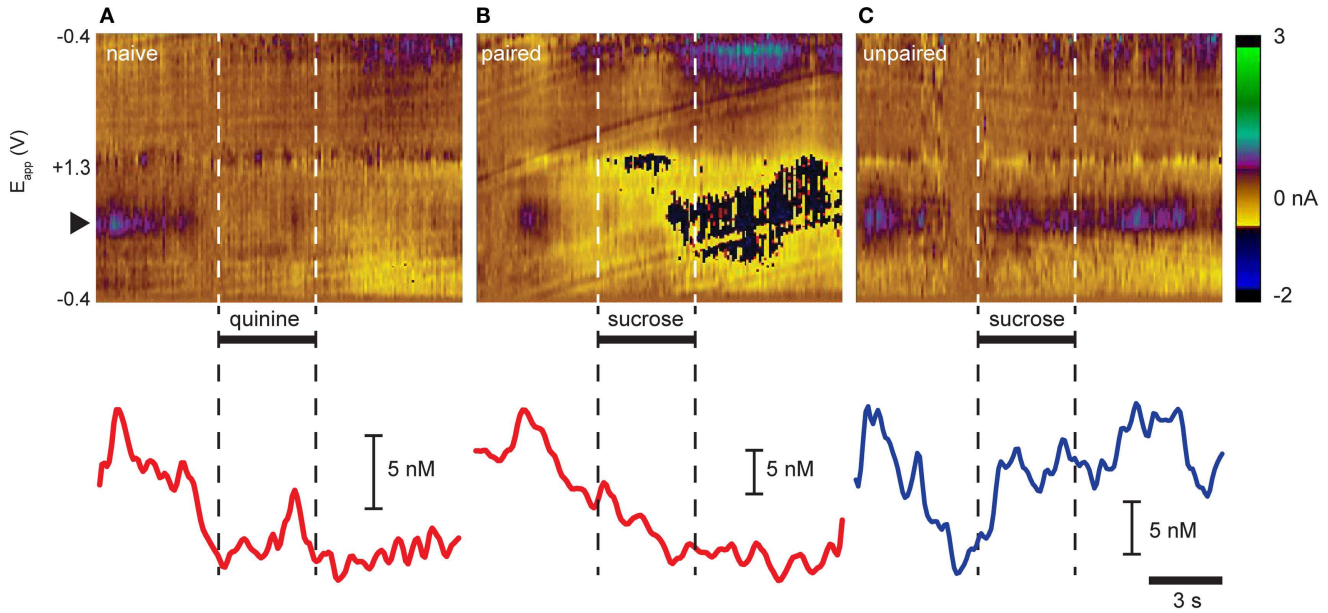

FIGURE 1 | Opposing effects of aversive and rewarding taste stimuli on dopamine release in NAc shell. Representative trial examples resulting from intra-oral infusions of **(A)** quinine in naïve rats, **(B)** sucrose in rats that had experienced sucrose explicitly paired with LiCl-induced malaise, and **(C)** sucrose in rats that did not have sucrose paired with malaise. Color plots (top panels) show changes in current (color) at different electrode potentials (*y*-axis) over time (*x*-axis). Dopamine is distinguished by its characteristic oxidation peak (∼0.6 V; black triangle; green/purple feature). Dopamine concentration traces (lower panels) are extracted from above using principal component analysis. Horizontal bars and dashed vertical lines indicate time of infusion.

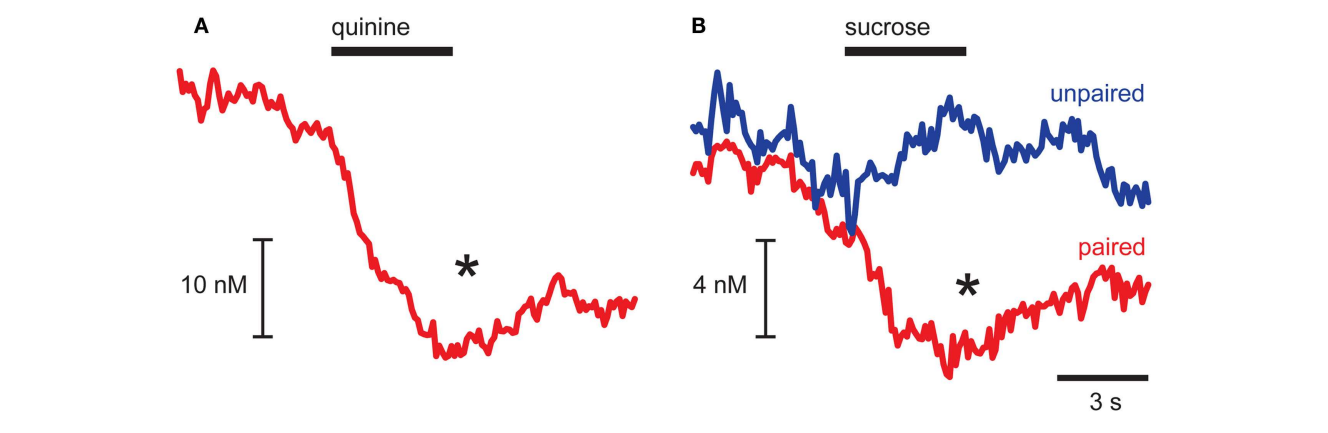

FIGURE 2 | Aversive stimuli suppress dopamine release in NAc shell. Averaged dopamine concentration traces showing suppression of dopamine release after quinine **(A)** and sucrose infusions in Paired rats [**(B)**, red trace] and no change in dopamine release in Unpaired rats [**(B)**, blue trace]. $*p < 0.05$ pre-infusion vs. infusion epoch.

supporting the existence of a population of dopamine neurons that are excited by aversive stimuli (Horvitz, 2000; Joshua et al., 2008; Brischoux et al., 2009; Matsumoto and Hikosaka, 2009). Emerging evidence supports anatomical segregation of dopamine neuronal responses (Brischoux et al., 2009; Matsumoto and Hikosaka, 2009; Bromberg-Martin et al., 2010; Lammel et al., 2011) in the midbrain with the conclusion that projection target is a key determinant of each cell's phenotype and response profile (Lammel et al., 2011). Fast-scan cyclic voltammetry captures fluctuations in dopamine concentration likely caused by phasic changes in electrophysiological activity (e.g., increases and decreases; Garris et al., 1997; Sombers et al., 2009; Owesson-White et al., 2012). As dopamine neurons extensively arborize (Matsuda et al., 2009), cylindrical carbon fiber microelectrodes used for voltammetry likely assay dopamine released from the terminals of different dopamine neurons and thus a net population terminal response. Suppression of phasic dopamine within the NAc shell has now been consistently reported for aversive taste stimuli. This strongly suggests that the

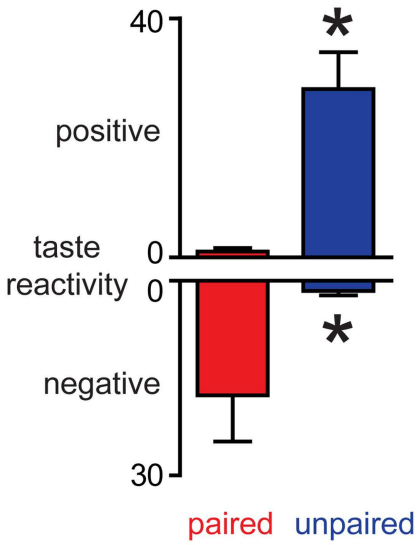

FIGURE 3 | Induction of conditioned taste aversion leads to a decrease in the palatability of sucrose. In Paired rats, sucrose infusions evoke more negative and less positive orofacial movements than in Unpaired rats. *$p < 0.05$ vs. Paired rats.

population response of NAc shell-projecting dopamine neurons to aversion is that of a decrease in activity.

We have shown here that aversive taste stimuli – those that are innately aversive or acquire aversive properties through conditioning – evoke average decreases in dopamine concentration within the NAc shell subregion. These data replicate (Roitman et al., 2008; Wheeler et al., 2011) and extend previous findings to a CTA paradigm. One difficulty with trying to reconcile studies of reward vs. aversion is that the stimuli used to elicit responses are often qualitatively different and cannot be directly compared. For example, how should an electric shock be treated relative to a sugar pellet? We have circumvented this issue by using taste stimuli, which allow reward and aversion to be studied when stimuli of different hedonic values are conveyed to the central nervous system via the same sensory modality. We deliver solutions directly into the animal's mouth via intra-oral catheter. Intra-oral delivery gives the experimenter exquisite control over stimulus timing allowing fast neurophysiological or neurochemical events to be correlated with sampling of the stimulus. Furthermore, animals can be exposed to stimuli without requiring a volitional movement thus removing another confound that besets many studies and allowing aversive stimuli that would normally be avoided to be effectively studied.

While we did not assay other striatal dopamine terminal regions, it is possible that responses differ with respect to dopamine terminal locations. Indeed, topographical specificity for responses to reward have been demonstrated (Aragona et al., 2009; Brown et al., 2011; Cacciapaglia et al., 2012). Early studies using microdialysis showed that the dopamine response to foot shock occurs with a greatly different time course in the prefrontal cortex than in the NAc (Abercrombie et al., 1989). Thus, future work will need to consider dopamine terminal sub territories in drawing conclusions about a role for dopamine in both reward and aversion.

IMPLICATIONS OF A PAUSE IN PHASIC DOPAMINE RELEASE IN THE NAc SHELL

Pauses in the electrophysiological activity of dopamine neurons likely underlie the pauses in dopamine release events we observed on single trials and the average decrease, relative to baseline, across trials in which rats experienced aversive taste stimuli. These pauses in dopamine release, in turn, are likely to have their strongest effects on D2 receptor-expressing medium spiny neurons (MSNs). D2 receptors are high affinity (Richfield et al., 1989) and are thought to be mostly occupied even during the asynchronous baseline firing of dopamine neurons that characterizes the absence of salient stimuli (Dreyer et al., 2010). Thus, a pause in dopamine release would lead to a reduction in D2 tone as D2 receptors become transiently uncoupled from dopamine. D2 receptor activation suppresses MSN excitability and the absence of D2 tone causes an increase in excitability (Surmeier et al., 2011). This is particularly interesting because there is strong and growing evidence that NAc neurons, and particularly shell neurons, are excited by aversive stimuli (Carlezon and Thomas, 2009). Tail pinch activates a majority of striatal neurons (Williams and Millar, 1990). Intra-oral infusions of aversive taste stimuli, identical to those used here, evoke primarily increases in the firing rate of NAc neurons (Roitman et al., 2005, 2010), particularly in the shell (Wheeler et al., 2008; Loriaux et al., 2011). In addition, D2 receptor activity has a prominent role in shaping the strength and direction of striatal synaptic plasticity and the absence of D2 receptor tone can shift the balance between long-term depression and long-term potentiation (Calabresi et al., 2007; Surmeier et al., 2011). Thus, pauses in dopamine release coupled with excitatory inputs evoked by aversive stimuli can lead to plasticity in D2 receptor-expressing MSNs and contribute to the learning of appropriate responses to aversive events. The focus on D2 receptor-expressing neurons is especially interesting since their increased activity has recently been shown to be aversive and promotes avoidance learning (Kravitz et al., 2012).

POTENTIAL MECHANISMS FOR SUPPRESSED PHASIC DOPAMINE RELEASE TO AVERSIVE TASTE STIMULI

Future work must address the mechanisms by which aversive stimuli in general, and taste stimuli specifically, suppress phasic dopamine signaling. Recent publications have focused on this question. Local GABA neurons that suppress the firing rate of VTA dopamine neurons are excited by foot shock in anesthetized rats (Tan et al., 2012) and air puff in awake mice (Cohen et al., 2012). The rostromedial tegmental nucleus (RMTg) is situated just posterior to the VTA, projects to and inhibits dopamine neurons, and is activated by foot shock (Jhou et al., 2009). Neurons within the lateral habenula are activated in response to aversive stimuli, project to the VTA and the RMTg, and contribute to pauses in the firing rate of dopamine neurons (Benabid and Jeaugey, 1989; Matsumoto and Hikosaka, 2007; Stamatakis and Stuber, 2012). It remains unclear, though, how aversive tastes may suppress phasic dopamine release. The parabrachial nucleus, which is the second central relay in gustatory processing, also contains neurons that increase in activity in response to foot shock, project to the VTA, and suppress dopamine neural activity (Coizet et al., 2010). It will be of considerable interest to determine if aversive taste-responsive parabrachial cells project to the VTA and similarly

suppress dopamine neural activity. Finally, NAc neurons project, in part, back to the VTA. We have shown that the kappa opioid agonist salvinorin A suppresses phasic dopamine release (Ebner et al., 2010). Since NAc neurons are mostly excited by aversive taste stimuli, dynorphin release leading to kappa receptor activation remains a strong possibility as well.

CONCLUSION

Here, we have reviewed literature and presented novel findings detailing the effect of brief aversive stimuli on the neuronal responses of midbrain dopamine neurons and dopamine release in terminal regions. Our data show that in one of these projection sites, NAc shell, the response to aversive stimuli is uniformly a suppression of spontaneous dopamine release. Importantly, the stimuli used were presented in the same modality as rewarding stimuli, which evoke increases in dopamine release. Future work will determine whether these patterns hold true for other projection regions.

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How costs influence decision values for mixed outcomes

Deborah Talmi [1] **** and Alex Pine*** [2]

[1] University of Manchester, Manchester, UK
[2] Department of Neurobiology, Weizmann Institute of Science, Rehovot, Israel

Edited by:
Jean-Claude Dreher, Centre National de la Recherche Scientifique, France

Reviewed by:
Mauricio R. Delgado, Rutgers-Newark: The State University of New Jersey, USA
Rafal Bogacz, University of Bristol, UK

****Correspondence:***
Deborah Talmi, School of Psychological Sciences, Coupland 1, University of Manchester, Oxford Road, Manchester M139PL, UK.
e-mail: deborah.talmi@manchester.ac.uk

The things that we hold dearest often require a sacrifice, as epitomized in the maxim "no pain, no gain." But how is the subjective value of outcomes established when they consist of mixtures of costs and benefits? We describe theoretical models for the integration of costs and benefits into a single value, drawing on both the economic and the empirical literatures, with the goal of rendering them accessible to the neuroscience community. We propose two key assays that go beyond goodness of fit for deciding between the dominant additive model and four varieties of interactive models. First, how they model decisions between costs when reward is not on offer; and second, whether they predict changes in reward sensitivity when costs are added to outcomes, and in what direction. We provide a selective review of relevant neurobiological work from a computational perspective, focusing on those studies that illuminate the underlying valuation mechanisms. Cognitive neuroscience has great potential to decide which of the theoretical models is actually employed by our brains, but empirical work has yet to fully embrace this challenge. We hope that future research improves our understanding of how our brain decides whether mixed outcomes are worthwhile.

Keywords: cost-benefit analysis, decision-making, decision-making and neuroeconomics, economic models, reward, punishment, aversive decision-making

When faced with many possible courses of action humans and animals must evaluate their expected future costs and benefits in order to decide optimally. Every action is associated with a cost because every action requires, at minimum, some energy expenditure for execution. The things that we hold dearest often require a sacrifice, as epitomized in the maxim "no pain, no gain." We struggle to be included in our peer group, study hard to increase our career prospects, work to provide for our families, pay to go on vacation, subject ourselves to painful health tests to maintain our physical well-being, and spend considerable energy on caring for our loved ones. Understanding how costs are integrated with benefits to ultimately reach a decision is therefore of paramount importance.

Value-based theories of decision-making suggest that people are thought to evaluate courses of action on the basis of their predictions about the future happiness a choice will engender (Von Neumann and Morgenstern, 1947; Vlaev et al., 2011). Because people are notoriously bad at predicting their future emotions (Hsee and Hastie, 2006) their decision utility is often different from their experienced utility at the time the consequences of their action come to fruition (Kahneman et al., 1997). Here we focus on decision utility, the time when agents decide between different prospects. Our question is how the subjective value of outcomes that are mixtures of costs and benefits is established.

We define costs and benefits as outcome attributes that decrease or increase, respectively, the decision value of that outcome at the time of decision-making. The costs and benefits most often studied in cognitive neuroscience include primary reinforcers such as food, drink, physical effort, and pain; secondary reinforcers such as monetary gains and losses; and mental events such as cognitive effort (Kool et al., 2010) and emotional suffering, such as the pain of regret (Bell, 1982). Although in some situations effort may be rewarding (Kivetz, 2003; Kim and Labroo, 2011), it is normally considered a cost (Hull, 1943).

While the definition of benefits is straightforward, our definition of costs may be controversial because it excludes some aversive outcome attributes. For instance, a decision may be risky because it entails a chance that a reward is not obtained, or it may prolong the time until reward is available for consumption. Yet we do not consider risk and delay to be true costs because they do not produce a negative subjective utility on their own, in the absence of other rewards or costs. Both risk and delay derive their meaning from the nature of the outcome and modulate its utility; their emotional valence depends on whether the outcome is rewarding or costly (see Loewenstein, 1987, for discussion on the valence of delay). As we will see, all available models of value integration make a similar distinction in that they treat risk and delay differently to "true" costs.

There are several theoretical valuation models for integrating costs and benefits. Cognitive neuroscience has great potential to decide which one is actually employed by the brain. Yet the burgeoning behavioral and neurobiological work on decisions between mixed outcomes often employs a single model of valuation, and model comparison work is rare. Our aim in this paper is to encourage empirical scientists to design behavioral and neurobiological experiments that can uncover the functional form of value integration in the brain.

In the first section we review the dominant model of value, which assumes an additive integration of costs and benefits. Alternative cost-benefit integration models draw substantially on our understanding of how risk and delay influence valuation. This influence is therefore reviewed briefly in the

second section. The third section describes alternative models of cost-benefit integration, all interactive in nature, with the aim of rendering them accessible for the neuroscience community. These three sections concentrate on theoretical models but draw on some pertinent behavioral work. In the final two sections we provide a selective review of relevant neurobiological work from a computational perspective, focusing on those studies that illuminate the underlying valuation mechanisms.

THE ADDITIVE MODEL OF VALUE INTEGRATION

A dominant model for cost-benefit decision-making is expected utility theory (Von Neumann and Morgenstern, 1947). Here the subjective value (V) of a choice is computed as the sum of the probability (p) weighted utility (U) of each of its possible outcomes:

$$V = \sum_{k=1}^{n} p_k \times U(m_k) \quad (1)$$

In this equation m signifies the magnitude of rewards and costs associated with the outcomes the choice entails. The utility function in this theory is typically plotted for positive ms where it is concave, with diminishing sensitivity for larger ms. Costs are represented by negative Us. This is an additive model of valuation because the disutilities of costs are summed with the utilities of beneficial outcomes. A positive V favors a decision to act, and if there is more than one option under consideration the action with the greatest expected utility is chosen.

The additive model of valuation is dominant, but there are a number of interesting alternatives (see **Table 1**; **Figure 1**). Crucially, there are situations in which the additive model may not be valid. Multi-attribute utility theory (Keeney and Raiffa, 1993), for example, allows additive integration only under the assumption of "additive independence" (Thurston, 2006). Consider a lottery where an agent may obtain one of two outcomes with a 50% probability. Both outcomes are a mixture of two attributes, x and y, each with two values – for example, a large sandwich for \$4 or a smaller sandwich for \$2. Under additive independence an agent who is indifferent between the two outcomes of Lottery A, $[x_2,y_1]$ and $[x_1,y_2]$ would also be indifferent between the two outcomes of Lottery B where the same attributes and values are recombined $[x_1,y_1]$ and $[x_2,y_2]$. Clearly, an agent who is indifferent between the possible outcomes of lottery A – the high-reward/high-cost outcome and the low-reward/low-cost outcome – is unlikely to be indifferent between the two outcomes of lottery B where the high-reward/low-cost outcome (a large sandwich for \$2) clearly dominates the low-reward/high-cost outcome (a small sandwich for \$4). In this scenario reward and cost are not additively independent, suggesting that they should not always be combined according to the additive model.

Before we describe alternative models of cost-benefit integration we discuss in a little more detail how risk and delay are thought to modulate the value of an outcome with either a rewarding or a costly attribute.

MODULATION OF COSTS AND BENEFITS BY RISK AND DELAY

Consider a patient who must evaluate a treatment option. The improvement in health this treatment brings and the painful procedure it involves must both be weighed against the chance that it is not efficacious and will only yield benefits after a long recovery period. In this section we discuss how risk and delay influence the subjective value of a reward or a cost.

MODELING RISK

Expected utility theory, a prescriptive model for decision-making under risk, fits empirical data less well than the descriptive Prospect theory (Kahneman and Tversky, 1979; Tversky and Kahneman, 1992). In Prospect theory utilities are again computed as a product of two functions, one transforming gains and losses (the utility function) and the other transforming given probabilities (the probability weighing function). The utility function is concave in the gain domain and convex in the loss domain with a steeper slope in the latter, so that the disutility of losses is greater than the utility of gains, allowing prospect theory to account for loss aversion. Prospect theory also proposes a non-fixed reference point for changes in utility, rather than a fixed point representing final wealth states; this feature is important for our discussion in Section "Modeling costs as right-shifts of the utility function". These transformations allow the theory to account for a number of expected utility violations, such as the reflection and framing effects and biases in the perception of small and large outcome probabilities (Kahneman and Tversky, 1979, 2000; Tversky and Kahneman, 1981). Both expected utility and Prospect theory entail a multiplicative integration of utility with its probability, such that utility is weighted (or discounted) in accordance with its decreasing likelihood of occurrence.

The form of probability discounting proposed by expected utility theory does not account adequately for an array of anomalies in decision-making under uncertainty, but prospect theory can account for most of those. The mathematical form of the probability weighting and utility functions in prospect theory are not formally specified beyond their qualitative predictions, but more precise formulations derived from a body of animal

Table 1 | Models of value integration.

Additive models	Interactive models
Expected utility theory: $V = p_r \times U(m_r) - p_c \times U(m_c)$	Trade-off model: $V = p \times U(m_r)/U(m_c)$
Prospect theory: $V = P(p_r) \times U(m_r) - P(p_c) \times U(m_c)$	Hyperbolic discounting: $V = U(m_r)/[1 + k \times U(m_c)]$
Discounted utility theory: $V = P(p_r) \times D(d_r) \times U(m_r) - P(p_c) \times D(d_c) \times U(m_c)$	Right-shift of the utility curve: $V = P(p) \times U(m_r - m_c)$
	Bilinear model: $V = x_1 \times U(m_r) - x_2 \times U(m_c) - x_3 \times U(m_c) \times U(m_r)$

The subjective value of a single mixed outcome with probability p, one rewarding attribute m_r and one costly attribute m_c (coded positively so that greater m_c represents greater cost), delivered after a time delay d. U, P, and D are functions that transform externally given quantities m, p, and d into internal representations. x_1, x_2, and x_3 are constants.

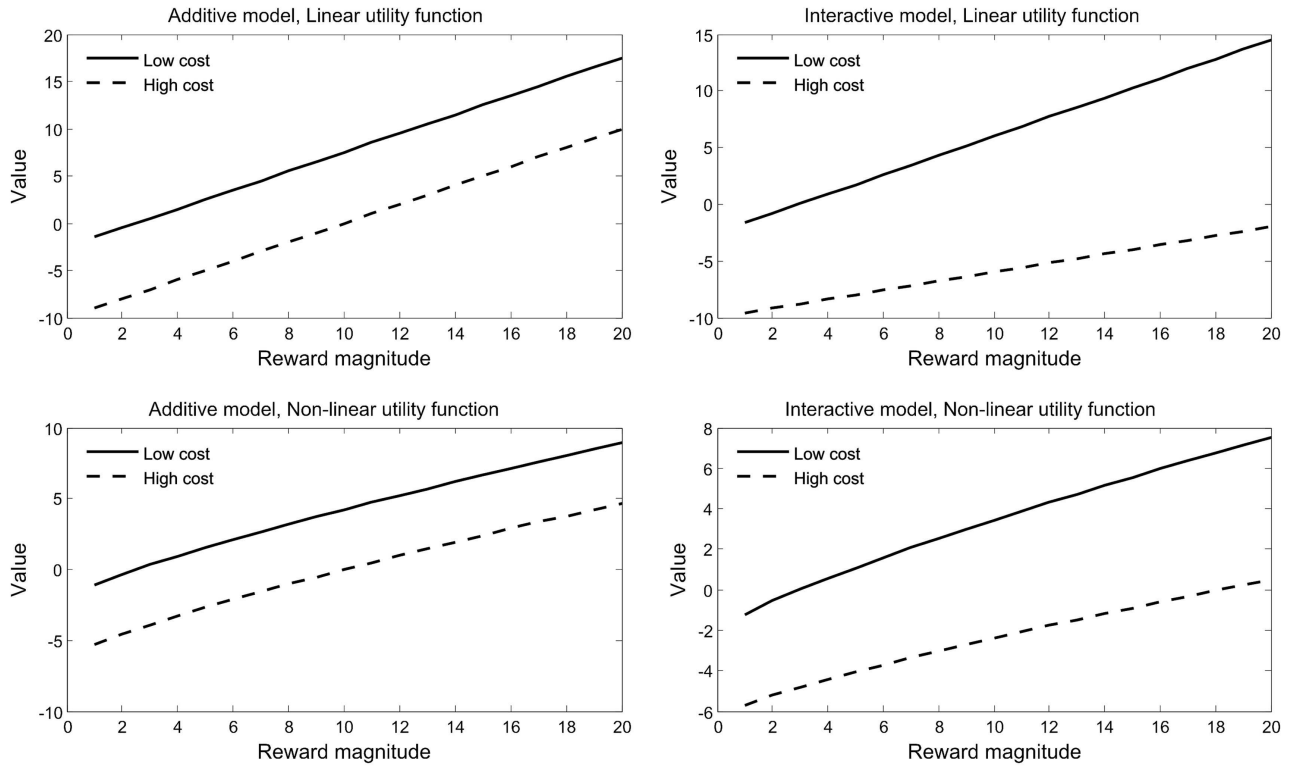

FIGURE 1 | Additive and. interactive models of value integration. Value was computed according to the bilinear model with $x_1 = 1$ and $x_2 = 1$. Additive models are depicted on the left, with $x_3 = 0$. Interactive models are depicted on the right, with $x_3 = 0.06$. Top panels employed a linear utility function for rewards and costs (those that were employed by Talmi et al., 2009); bottom panels employed a power function with exponent 0.8. Additive models with non-linear utility (bottom left) represent the predictions of expected utility theory with $p = 1$. Figure adapted from Park et al. (2011).

and human probability discounting experiments indicate that probabilistic rewards are discounted in a hyperbolic or quasi-hyperbolic manner as their likelihood diminishes (Green and Myerson, 2004; Green et al., 2004, 2011). These experiments typically employ psychophysical, "adjusting amount" procedures (Rachlin et al., 1991). In a standard procedure, participants are required to choose between a smaller-certain reward and a larger-probabilistic reward. In each trial the amount of the smaller reward is adjusted until the participant is indifferent between the two options. Under the assumption that indifference entails equality of subjective value the subjective value of the risky option can be quantified in terms of the certain (risk-free) option. The probability of the larger reward is then altered such that the probability discount function can be estimated from a number of indifference points across the probability spectrum. Results of these procedures consistently show that hyperbolic functions provide a superior fit to these indifference points, in contrast with the predictions of expected utility theory (**Figure 2**). To take this into account p in Eq. 1 can be replaced by $P(p)$ where

$$P(p) = \frac{1}{1 + h \times \Theta} \tag{1.1}$$

With

$$\Theta = \frac{1 - p}{p} \tag{1.2}$$

Θ is termed the "odds ratio" and is computed as the probability of non-occurrence divided by the probability of occurrence. An odds ratio of 1 therefore corresponds to outcomes that occur 50% of the time. h is a discount rate parameter which determines the rate of probability discounting. If $h = 1$ the individual is risk neutral and values the reward in accordance with EU theory, so $P(p) = p$. When $h < 1$ the individual is described as risk averse $[V < (p \times M)]$ and when $h > 1$ as risk seeking (**Figure 2**). $P(p)$ can be considered as a discount factor between zero and one by which the reward is discounted in accordance with its "odds against."

The main feature of a hyperbolic discount function is that the reward loses a gradually smaller proportion of its value per increasing unit in odds against – so it loses a larger proportion of its value when the probability changes from 90 to 80% than when it changes from 60 to 50%. This can explain why a person who chooses a smaller but more certain reward over a larger but more risky option can switch their preferences when the probability of both options is reduced by a constant – similar to the Allais or certainty paradox (Allais, 1953; Kahneman and Tversky, 1979). The smaller (below 1) is h, the greater is the steepness of the initial devaluation relative to the later devaluation. Note that this formulation is consistent with the predictions of prospect theory, for example, the overweighting of events with small probabilities and the underweighting events with large probabilities (**Figure 2**). A number of similar but more complex functions have been proposed that

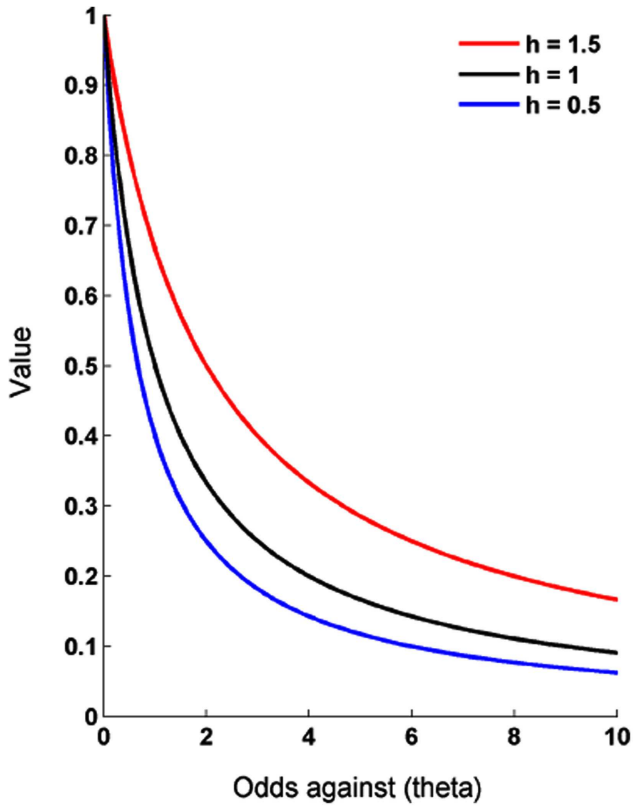

FIGURE 2 | Hyperbolic discounting of risk. In this basic hyperbolic model individuals steeply discount reward value with initial decreases in probability of occurrence and only gradually as they get more unlikely. *h* is a risk aversion parameter. In the case of $h = 1$ discounting conforms to EU theory, i.e., an equal decrease in value for every percent decline in probability. $h < 1$ equates to risk aversion and when greater than one to risk seeking. Value here is represented as a proportion of its initial (certain) value or alternatively as the discount factor.

attempt to capture other features of subjective valuation by adding extra parameters (Green and Myerson, 2004; Myerson et al., 2011).

MODELING DELAY

While it is difficult to extend EU and prospect theory to account for situations where people choose between rewards or punishments that are available at different points in time (termed intertemporal choice), discounted utility theory models this situation explicitly. The subjective value of a single, certain outcome m that is delayed by d can be expressed as

$$V = D(d) \times U(m) \tag{2}$$

With $U(m)$ representing the instantaneous utility of m and $D(d)$ representing a discount factor ranging from zero to one by which $U(m)$ is discounted in accordance with its objective delay.

In fact, the probability discounting approach outlined above derives from an older and richer literature on temporal discounting (Loewenstein and Elster, 1992; Frederick et al., 2002; Green and Myerson, 2004), and relates to a debate as to which is the primary discounting mechanism – probability (because delay entails uncertainty) or delay (because the resolution of uncertainty takes time, Prelec and Loewenstein, 1991; Rachlin et al., 1991). In discounted utility theory the utility of a reward is discounted exponentially as a function of its delay, namely with a constant percentage decrease in value per unit time (Samuelson, 1937; Koopmans, 1960).

$$D(d) = \mathrm{e}^{(-k*d)} \tag{2.1}$$

k is a free parameter which represents the individual's discount rate. Thus k quantifies an individual's tendency to discount future costs and benefits. An individual with a high k value devalues future costs and benefits more steeply than a lower k individual, i.e. with a greater percentage decrease in value per unit time. k is thought to relate to impulsivity in the same manner as h relates to an individual's risk profile (Ainslie, 1975, 2001) because individuals with a large k are more likely to choose the smaller-sooner over larger-later option.

Although people do discount exponentially in some situations (Schweighofer et al., 2006), there is a wealth of empirical evidence against exponential discounting, primarily in the robust finding that the discount rate is not constant but decreases with time. In a simple demonstration (Thaler, 1981) asked subjects to specify the amount of money they would require in 1 month, 1 year or 10 years to make them indifferent between that option and receiving $15 now. Their median responses ($20, $50, $100) implied an average annual discount rate of 19% over a 10 year horizon, 120% over a 1 year horizon and 345% over a 1 month horizon. Similar observations have been made for in non-monetary domains such as health and credit markets (Redelmeier and Heller, 1993; Chapman and Elstein, 1995; Chapman, 1996, 2001; Pender, 1996). A noted manifestation of this feature is that humans and animals are prone to preference reversals when a constant delay is added to both options of an intertemporal choice (Prelec and Loewenstein, 1991; Loewenstein and Elster, 1992). For example, people who prefer $10 today over $11 tomorrow often also prefer $11 in 31 days to $10 in 30 days (Green et al., 1994). As we have seen, the same reversals also characterize choices between certain and probabilistic outcomes.

When mathematical functions are fit to intertemporal choice data (for example indifference points between smaller-sooner and larger-later options) a multitude of studies have demonstrated that hyperbolic or quasi-hyperbolic discount functions provide a superior fit compared to exponential functions in both humans and animals, for delayed monetary, health-related, and other forms of reward, and punishment (reviewed in Rachlin et al., 1991; Ho et al., 1999; Frederick et al., 2002; Green and Myerson, 2004, but see Kable and Glimcher, 2007, for a different model). The standard and most widely used functional form for hyperbolic discounting in the behavioral literature was proposed by Mazur (1987) and based on earlier work by Ainslie and Herrnstein (1981), Ainslie (1975), Herrnstein (1981). According to this work,

$$D(d) = \frac{1}{1 + k \times d} \tag{2.2}$$

so that

$$V = \frac{m}{1 + k \times d} \tag{2.3}$$

If we taker $U(m)$ to be a better representation of the instantaneous value of M (Pine et al., 2009) then

$$V = \frac{U(m)}{1 + k \times d} \tag{2.4}$$

As with probability discounting, other functional forms which capture decreasing rates of discounting and the non-linearity of the relationship between objective and subjective delay have also been proposed (Phelps and Pollak, 1968; Loewenstein and Prelec, 1991; Frederick et al., 2002; Green and Myerson, 2004; Myerson et al., 2011).

Expected utility, prospect theory and discounted utility theory entail an attenuation of reward sensitivity with risk or delay. This means that when reward is risky or delayed, the utility gained by increasing it by a constant reduces, so that $U(m+1) - U(m)$ is greater than $U(m+1) \times D(d) - U(m) \times D(d)$ or $U(m+1) \times P(p) - U(m) \times P(p)$. **Figure 3B** illustrates this point. By combining these forms of discounting, the subjective value of either costs or benefits can also therefore be represented as a product of utility with two discount factors, one based on probability and the other on delay (Prelec and Loewenstein, 1991; Rachlin and Raineri, 1992; Ho et al., 1999):

$$V = \sum_{k=1}^{n} P\left(p_k\right) \times D\left(d_k\right) \times U\left(m_k\right) \tag{2.5}$$

ALTERNATIVE MODELS FOR THE EFFECTS OF RISK AND DELAY

A key challenge for the models we presented for the integration of reward with probability and delay (Eq. 2.5) concerns the effect of reward magnitude on valuation. The "magnitude effect" refers to a prevalent finding in intertemporal choice that small magnitudes are discounted more steeply than large ones. A person who is indifferent between \$60 today and \$120 in 1 year is thus more likely to choose \$1200 in 1 year to \$600 today. The magnitude effect has been documented in numerous studies involving both real and hypothetical rewards (reviewed in Frederick et al., 2002; Green and Myerson, 2004) For instance, Thaler (1981) asked his participants to decide between a given immediate monetary reward and a delayed monetary reward they would receive in a year's time. Participants were required to declare how much money they would want in a year for them to be indifferent between the immediate and the delayed options. He found that the immediate amounts of \$4000, \$350, and \$60 were discounted by 29, 34, and 39%, respectively. Although the magnitude effect has also been documented in non-monetary reward domains such as medical treatments, drugs, job choices, vacations, and restaurant tips (Raineri and Rachlin, 1993; Chapman and Elstein, 1995; Chapman, 1996; Chapman and Winquist, 1998; Baker et al., 2003; Schoenfelder and Hantula, 2003) it has not been observed in species other than humans, for example in rats and pigeons and primates using food rewards (Richards et al., 1997; Grace, 1999; Green and Myerson, 2004; Freeman et al., 2012, but see Grace et al., 2012). In humans the magnitude effect has not been reliably observed in the loss domain (Estle et al., 2006) and in some (but not all) studies seems to level off when the magnitudes involved are fairly large (Shelley, 1993; Green et al., 1997).

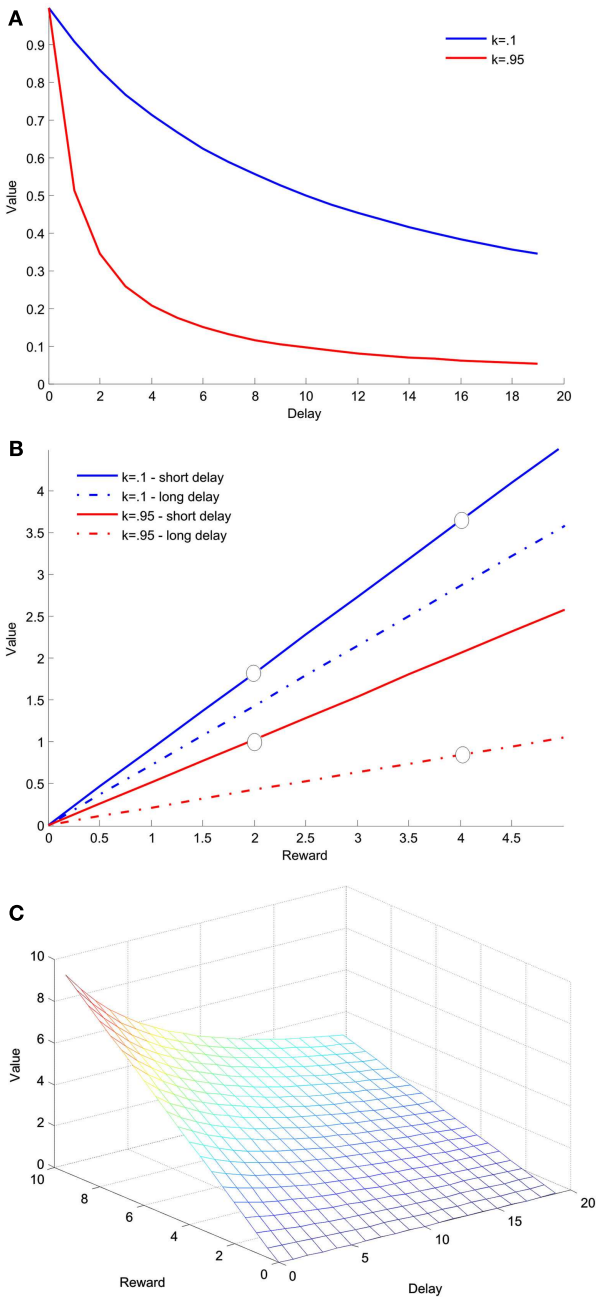

FIGURE 3 | Hyperbolic discounting of delay. This function describes theoretical data from an experiment in which two groups of animals are given a choice between two arms of a maze, one of which contains a larger-later reward, four food pellets that necessitate a wait of 15 s, and one which contained a smaller-sooner reward, two food pellets that were available after 3 s. **(A)** Value as a function of delay for a single reward magnitude, two food pellets, computed according to Eq. 2.3. The discount function is depicted for two values of k with higher k indicating steeper, (more impulsive) discounting. **(B)** Value as a function of reward magnitude for the two different and delays, 3 and 15 s, computed using the same equation. The circles show the two options presented to the two groups of animals. In this example the value of the larger-later reward is greater for the less impulsive group, and the value of the smaller-sooner reward is greater for the more impulsive group. **(C)** Value as a function of both delay and reward magnitude.

Although less explored, there is evidence that reward magnitude has the opposite effect on probability discounting compared to temporal discounting. The "peanuts effect" describes the finding that larger magnitude rewards are discounted more steeply than smaller rewards, implying that people tend to be less risk averse when they are "playing for peanuts" (Weber and Chapman, 2005; Chapman and Weber, 2006). For example, an individual may prefer a 10% probability of obtaining $100 over a certain $10, but may also prefer a certain $100 to a 10% probability of winning $1000. The reward magnitude effect humans display when they evaluate risky and delay outcomes poses a challenge for the multiplicative $P \times D \times U$ approach in Eq. 2.5, since it suggests that D and P themselves depend on U. The double dissociation between the effect of reward magnitude on delay and probability exacerbate the challenge because it suggests that magnitude effects cannot simply be explained by a property of the discount function U. We briefly review two approaches to this challenge and in Section "Using Neurobiological Evidence to Decide Between Models of Risk and Delay" we discuss how neurobiological data can help decide between them.

Green and Myerson (2004), Myerson et al. (2011) posit that magnitude scales the temporal discount rate parameter k in Eq. 2.3 such that k decreases with increasing magnitude. By contrast, in probability discounting magnitude scales an exponent of the denominator of the discount function in Eq. 1.1. Because this renders the two discount functions D and P partially a function of m, the subjective value V can no longer be thought of as the product of a multiplication of separate utility and discount functions U, D, and P.

Prelec and Loewenstein (1991) offer a general scheme with which to view multi-attribute choice. Their model, an extension of prospect theory, similarly relies on the decomposition of valuation into separate discount and utility functions, and explains magnitude effects in delay discounting in terms of the utility function. They suggest that agents represent or "frame" each attribute of a multi-attribute outcome as a pair of values. The first value is the absolute magnitude of the attribute and the second is what they call the "polarity," namely, whether it is beneficial or detrimental. For example, $50 in 2 weeks is encoded as $(50, 2)$ with the polarities $(+, -)$. The importance of attributes relative to each other can be altered by certain linear transformations. One such linear transformation is adding a constant to the magnitude of all values of an attribute. The consequence of this transformation is "decreasing absolute sensitivity," a decrease in the importance of that attribute relative to others. A second transformation involves multiplying all values of an attribute by a constant. The consequence of this transformation is "increasing proportional sensitivity," an increase in the importance of that attribute. The magnitude effect in intertemporal choice follows from increasing proportional sensitivity because multiplying the monetary attribute increases its importance relative to the delay attribute, leading to the appearance that larger magnitudes are discounted less. These features of multi-attribute framing can explain many of the anomalies common to decision-making under uncertainty and intertemporal choice. Yet because increased proportional sensitivity will always increases the importance of the monetary attribute this effect cannot explain the opposite effects of reward magnitude on delay and probability discounting.

To account for the peanuts effect Prelec and Loewenstein (1991) invoke "interaction effects." These are emotional processes that can influence cost-benefit decisions by changing the importance of the attributes of an outcome through valuation processes unrelated to utility and discount functions (Berns et al., 2007). Disappointment, one of many interaction effects, accounts for the magnitude effect in probability discounting. The notion here is that anticipation of disappointment – should a losing outcome occur – increases the greater the potential gain, and that increasing disappointment decreases the importance of the money relative to the probability attribute in a manner that accounts for preference reversals (Prelec and Loewenstein, 1991; Weber and Chapman, 2005; Chapman and Weber, 2006). Disappointment does not enter into delay discounting since there are no probabilistic outcomes. Interaction effects are useful, however, when we consider other interesting phenomena in intertemporal choice. The interaction effects of anticipation and dread are invoked to explain why in some cases people prefer to speed up punishments to "get them over with," and savor rewards by delaying them, phenomena which are incompatible with standard discounted utility theory (Loewenstein, 1987; Berns et al., 2006).

In summary, the discounted utility theory notion of a decision value-based on the multiplication of separate utility and discount functions has been challenged in light of opposing magnitude effects. In one view discount functions accept magnitude as an argument, with no requirement for a separate utility function. Although two separate mechanisms are required to account for opposing magnitude effects this is perhaps a more parsimonious account, but it does not explain a host of other influences on valuation that are captured by interaction effects. In another view additional mechanisms are invoked with magnitude solely acting on the utility function, and delay and risk are treated within separate weighting functions.

INTERACTIVE MODELS OF VALUE INTEGRATION

While the functional form of decision-making that involves risk and delay costs is well described, and a rich empirical literature delineates the neurobiology of effort-based decision-making (Salamone et al., 2007; Floresco et al., 2008a; Kurniawan et al., 2011), less research has been devoted to uncovering the functional form of valuation when effort and other costs are mixed with reward. In this section we review non-additive models for decision values when outcomes include costs. Because the empirical evidence for these models is more limited than that of the additive model we describe them within the context of experiments that corroborate them. Our aim is to expose these models for scrutiny by the neuroscience community and encourage further model comparison work to decide between them. **Table 1** lists all the valuation models discussed in this paper.

A strong alternative to the additive model is the trade-off model (Simonson, 1989), where decision values are expressed as the ratio of costs and benefits. The subjective value of a single mixed outcome with probability p, one rewarding attribute m_r and one costly attribute m_C, could be expressed as:

$$V = p \times \frac{U(m_r)}{U(m_C)} \tag{3}$$

Let us take two examples to illustrate how this model has been employed. Soman (2004) used the trade-off model to account for the results of an experiment where participants made hypothetical decisions between differently priced products that required more and less effort, such as an expensive desk that was already assembled and a cheaper desk that required customer assembly. Soman did not utilize model comparison but the trade-off model fitted his data well and accounted for the influence of delay on choosing between these mixed outcomes. Another example comes from work on foraging, where both the additive and the trade-off models are prevalent (Stephens and Krebs, 1986). Bautista et al. (2001) modeled cost-benefit decisions of starlings deciding how to forage for food: to walk (low-reward/low effort) or fly (high-reward/high effort). In that set-up rewards consisted of the energy gain from the food, and costs consisted of the energy loss associated with the chosen travel method. The authors compared the additive model and the trade-off models, which they termed net rate and efficiency, respectively, and found that the additive model accounted best for the starlings' decision.

One key difference between the additive and trade-off models is how they treat situations that do not offer any reward but impose a cost. The additive model allows subjective values to become negative in these situations, while the trade-off model does not. The importance of this feature depends on the situation. While non-rewarding decisions – between two costs, or a cost and the *status quo* – are rare in economic studies, they are common outside the laboratory. Berns et al. (2008) used an example of a patient deciding between risky treatment options, where the best outcome is maintaining current levels of health, and contended that it is difficult to explore such decisions in typical financial decision-making experiments because people are unlikely to take part in a study where they might end up losing out financially. The difficulty with financial costs is partially ameliorated in experiments that require participants to exert effort or suffer experimentally induced pain, although here too there is an implicit, unmodelled reward that draws participants to take part in the experiment in the first place. Clearly, though, according to the trade-off model the patient's decision or its laboratory equivalents, do not have a negative decision utility. The next models of valuation that we review differ in their approach to decisions between costs. The first does not model negative utilities in the absence of reward, the second predicts negative utilities, and the third allows for either zero or negative utilities. Therefore, in decisions between "bad" and "worse" an empirical demonstration of negative decision utilities will constrain model selection.

Another key difference between the additive and the trade-off models is whether reward sensitivity changes with costs. This is an important and under-appreciated difference between models. The additive model predicts that costs do not alter reward sensitivity, while the trade-off model predicts that they do. The models we review below differ in this respect too. The first predicts decreased reward sensitivity with cost, the second predicts increased sensitivity, and the third allows changes in either direction. Measuring changes in reward sensitivity is therefore another assay for model selection. Taken together, three aspects of the decision – whether it adheres to the additive independence assumption, the presence or absence of negative decision utilities, and whether reward sensitivity changes with cost – distinguishes integration across costs and benefit from valuation of all-rewarding multi-attribute outcomes.

HYPERBOLIC DISCOUNTING OF REWARDS ASSOCIATED WITH COSTS

Brañas-Garza et al. (2012) report a result that illuminates the social importance of understanding decision values of mixed outcomes in the field of health. When people consider a painful medical procedure their decision values should integrate over the pain costs of the procedure as well as the value of consequent future health benefits. How steeply one discounts the future will therefore impinge on the integrated value of the procedure. They found that the more impatient participants, those that discounted the future more steeply in an intertemporal choice task, reported more frequently that they experience a negative feeling as soon as they decide to undergo the procedure. This feeling may derive from the disutility of the decision value, and bias these participants against some health-promoting behaviors such as necessary painful medical procedures.

The success of the hyperbolic discount functions in accounting for the effect of delay and risk costs on choice makes it rather tempting to consider whether other costs devalue reward hyperbolically. The subjective value of a single, certain, mixed outcome with one rewarding attribute m_r and one costly attribute m_c, could be expressed as:

$$V = \frac{U(m_r)}{1 + k \times U(m_C)} \tag{4}$$

Prevost et al. (2010) used hyperbolic discounting (Eq. 2.4) to model how participants decided between cost-benefit mixtures. Participants first viewed fuzzy erotic images and then decided between two options: either viewing a clear image of the same content for a low-cost, or viewing it for a longer duration for a higher cost. The low-cost involved a short wait or exerting minimal physical effort, while the high-cost involved waiting longer or exerting more effort. The hyperbolic discount function described choices equally well for both delay and effort cost, and fared better in doing so than the exponential discount function.

We have seen that hyperbolic models are not ideal for situations that require a cost without providing a reward, because they do not allow negative decision utility when only costs are on offer. However, all trials in the paradigm used by Prevost et al. (2010) included at least a small reward, possibly contributing to the fit of this model for their data.

Clearly, if effort also modulates $U(m_R)$ hyperbolically, reward sensitivity will decrease under effort. But a hyperbolic interaction of effort with reward may not be detected in studies that only consider a linear form of interaction. Kurniawan et al. (2010), for example, obtained a different result from Prevost et al. (2010) in a task that similarly required participants to choose between a low-reward, low effort option and a large reward, large-effort option. Both effort and reward had the expected effect on decisions, and a similar effect on ratings of choice likability, but the interaction between reward and effort was not significant for either measurement. The null interaction effect appears to go against interactive models, but as Kurniawan and colleagues used the general linear

model in their analysis it is possible that they could not detect a non-linear interaction between effort and reward.

Prelec and Loewenstein (1991) speculated that their rules for transformation of attribute weighting should apply to all multi-attribute choices. Consequently, if effort and pain discount reward hyperbolically it would be natural to predict that effort and pain discounting will resemble risk and delay discounting, and generate preference reversals when a constant is added to both options. In decisions between outcomes that mix reward and pain, for example, adding a constant amount of pain to both options should shift preference in favor of the high-reward high-pain option. This is an example of how consideration of underlying models yields useful hypotheses for experimentation.

MODELING COSTS AS RIGHT-SHIFTS OF THE UTILITY FUNCTION

In prospect theory, choice options are coded as gains and losses relative to the "status quo," a neutral point of reference that is assigned a value of zero on the reward magnitude axis and is where the utility function crosses that axis (Kahneman and Tversky, 1979). Utility is zero when people do not expend any effort, and therefore do not expect to be rewarded. Kivetz (2003) argued that effort requirements create an expectation for reward, which should be modeled as a right shift of the reference point. For example, when Thea is asked to mow the lawn she forms an expectation for reward. Agreeing to do this chore has a negative decision utility and is experienced as a loss relative to her revised reference point. If she is promised $5 for completing this chore and considers this sum fair this reward merely brings her decision value back to zero.

Prospect theory can be extended to account for effort costs by shifting utility function to the right under effort (Kivetz, 2003). People who expend effort $U(m_{c0})$ expect a fair reward, $U(m_{r0})$ in return. According to this formulation people should be indifferent between no reward/no effort and $U(m_{ro})/U(m_{c0})$. Kivetz (2003) was interested in frequency programs such as frequent-flyer miles, a marketing tool that requires customers to invest effort for future rewards. He showed that replacing $U(m)$ in Eq. 1 by $U(m_r{-}m_c)$ provided an adequate account for customers' choices and for the influence of risk on their decisions. The subjective value of a single mixed outcome with probability p, one rewarding attribute m_r and one costly attribute m_c, could be expressed as:

$$V = P(p) \times U\,(m_r - m_C) \tag{5}$$

Because of the concavity of U, right-shifting it under effort means that U now increases more steeply with m_R. Consequently, this model implies that effort increases reward sensitivity. For example, Thea may be just a little more delighted with a gift of $10 than $5, but after she is asked to mow the lawn her increased happiness with $10 relative to $5 is greater.

Kivetz (2003) argued that his model can be extended to all costs that people perceive as having an inherent disutility, and mentions delay and pain costs. Beyond the conceptual problem of considering the passage of time as inherently negative we would argue that the empirical evidence base for decreased reward sensitivity with delay (**Figure 3**) means that Kivetz' model, which predicts increased sensitivity under cost, is unlikely to account well for intertemporal choice.

A BILINEAR MODEL FOR COST-BENEFIT ANALYSIS

Phillips et al. (2007) based their proposed valuation model on their review of animal research concerning the role of dopamine in cost-benefit analysis. Their model was intended to be applicable for delay, effort, risk, and other aversive outcomes. They did not provide the functional form of the value function, perhaps because there is limited evidence for two of the central components of their model, namely, exactly how dopamine levels and the indifference functions vary with reward magnitude. Noting these reservations, and making some assumptions of our own, we derived their value function (Appendix). The function we derived in this way is somewhat unwieldy. However, for small rewards, within the linear portion of the utility function, their model can be expressed more simply as:

$$V = x_1 \times U\,(m_r) + x_2 \times U\,(m_C) + x_3 \times U\,(m_r) \times U\,(m_C) \tag{6}$$

With positive constants x_1 and x_2, and a constant x_3 that can be either positive or negative. Thus, although the value function proposed by Phillips et al. (2007) may appear to model value additively (Botvinick et al., 2009), a closer look shows that it includes an interaction between reward and cost, albeit of a different form than that in Eqs 3–5. **Figure 1** depicts this model and compares it to the additive model both for a linear and for a non-linear utility function.

Two aspect of the bilinear model are important for our discussion. First, in contrast with the other models discussed here this model allows reward sensitivity to either increase or decrease when outcomes include costs. The direction of change depends crucially on the functional forms of the reward utility function and the indifference function (see Appendix). Second, in contrast to the models in Eqs 3 and 4 this model allows utility to become negative when the choice options do not offer any reward.

Although Phillips et al. (2007) offered a very specific functional form to describe the interaction of rewards, costs, and value, they did not describe direct empirical evidence for that particular form. Two studies that examined decisions involving pain costs observed that the bilinear interaction model fitted their data well. In the first study (Talmi et al., 2009) participants chose between two options, one that maximized and one that minimized the chances for the delivery of a mixed outcome. That outcome included a monetary gain or a loss as well as an electrical stimulation of the skin that could be either painful or mild. Participants experienced the pain a few seconds after they made their choice, at which time they were also informed that the promised amount of money was added to their account. When Talmi and colleagues compared the additive model with the bilinear interaction model they found that the addition of an interactive term significantly improved the model fit, with the interaction parameter x_3 suggesting that physical pain attenuated the sensitivity of participants to monetary reward. This conclusion was corroborated by another study (Park et al., 2011) where participants were asked to accept or reject mixed outcomes that involved varying monetary reward and one of five pain magnitudes. The authors replicated Talmi et al.'s (2009) finding that the bilinear model accounted for, behavioral choice better than the additive model. Notably, participants in both studies likely experienced disutility in some of the experimental trials, because Talmi

et al. paired pain with either gains, losses, or zero rewards, and Park et al. used a very low amount of 1 cent in some of the trials, paired with both low and high levels of pain. This aspect of their paradigm may explain the importance of the parameter x_2 in their data.

While Talmi et al. argued that because the monetary rewards were very small, under $0.60, the utility of reward and the disutility of pain should be modeled linearly (Rabin and Thaler, 2001), Park et al. (2011) tested this hypothesis formally. Although they also employed small monetary rewards, up to €0.99, they found that modeling reward utility using a power function explained their data better than when a linear function was used. When this change was implemented, behavioral choice data no longer favored the bilinear over the additive model. Their fMRI results, however, fit the bilinear model better than the additive model regardless of whether reward utility was modeled with a linear or a power function. **Figure 1** (adapted from their **Figure 2**) compares four models: two interactive models, computed either with a linear or a non-linear utility function, and their additive model counterparts, which are identical but omit the interaction term. In fact, a detailed analysis of the bilinear model suggests that the importance of the interaction term depends on the relationship between the utility functions for rewards and costs, and is likely not to be important when they are identical. In order to decide, for a particular situation, whether an interaction term is present it is sufficient to determine the form of three functions: the utility function of rewards without costs; the utility function of costs without rewards; and the indifference function – the relationship between rewards and costs. In future work we plan to investigate the conditions for an interaction in more detail.

In summary, while the additive model is dominant in the economic literature, there are several alternative models that feature an interaction between costs and benefits such that costs alter sensitivity to reward. According to four of these models, described in this section, costs modulate the subjective utility of mixed outcomes. Each of these models proposes a different functional form to describe this interaction. Further empirical work can help determine which model best captures the decision values of mixed outcomes in animals and humans. In Section "Using Neurobiological Evidence to Decide between Additive and Interactive Valuation Models" we explore how neurobiological data can assist in this endeavor, but first we explore how such data can shed light on the modulation of costs and benefits by risk and delay.

USING NEUROBIOLOGICAL EVIDENCE TO DECIDE BETWEEN MODELS OF RISK AND DELAY

A large amount of empirical work in animals has been dedicated to uncovering the neural structures that mediate decision-making when mixed outcomes involve both costs and benefits. There is strong evidence in human neuroimaging for an abstract representation of subjective utility in the ventromedial prefrontal cortex (vmPFC) across many different kinds of commodities (Padoa-Schioppa, 2011; Levy and Glimcher, 2012), but controversy on where this abstract representation is expressed in animals (Padoa-Schioppa, 2011; Roesch and Bryden, 2011). The regions involved in the effects of delay, risk, and effort on decision-making have been described, with more limited investigations of other costs (Phillips et al., 2007; Salamone et al., 2007; Floresco et al., 2008a; Roesch and Bryden, 2011). Much of this literature, however, does not speak directly to the issues we focus on here, the functional form of integrative valuation of mixed outcomes. In this section we examine how empirical neurobiological data could help decide between the models for the modulation of costs or benefits, separately, by risk and delay. In the final section we discuss data relevant for models of cost-benefit integration.

EVIDENCE FOR SEPARATE REPRESENTATIONS OF *D* AND *U*

Animal and human neuroimaging studies have identified a relatively large set of regions that are involved in intertemporal decision-making (for reviews in animal studies see Cardinal et al., 2004; Winstanley et al., 2006; Floresco et al., 2008a,b; and in humans Tanaka et al., 2004, 2007; McClure et al., 2004, 2007; Kable and Glimcher, 2007; Gregorios-Pippas et al., 2009; Luhmann et al., 2008; Ballard and Knutson, 2009; Wittmann et al., 2007; Prevost et al., 2010; Hariri et al., 2006; Pine et al., 2009, 2010. They include ventromedial and medial prefrontal cortex, dorsal, and ventral striatum (VS), posterior cingulate cortex, and insula, as well as dorsolateral PFC, amygdala, and lateral OFC. There is no agreement on the particular contribution of each region to intertemporal choice and value construction. Recent literature has started to address regional specificity by correlating behaviorally derived model parameters with BOLD responses or single cell electrophysiological recordings. We will demonstrate how this approach has led to an increasingly sophisticated view of functional specificity and model implementation in the brain in animal electrophysiological recording and human neuroimaging studies.

McClure et al. (2004) performed the first neuroimaging study of intertemporal choice to provide a neurobiological account of temporal discounting and preference reversals. The disproportionate valuation of rewards available in the immediate future, and other evidence, led them to postulate the differential activation of distinguishable neural systems – specifically, that impatience is driven by the limbic system which responds to immediate rewards and is less sensitive to the value of future rewards, whereas patience is mediated by the lateral PFC which is able to evaluate tradeoffs between more abstract rewards, including those in the more distant future. This proposed struggle between an affective and a deliberative decision-making system was based theoretically on a quasi-hyperbolic time discounting function which splices together two different discounting functions, one exponential and another which distinguishes sharply between present and future rewards, modeled by a parameter termed beta. Beta represents the special value placed on immediate rewards relative to those received at any other time. The hypothesis then was that activity in lateral PFC areas should correspond with the rational, deliberative processes, and limbic activity should represent the beta parameter. To test this hypothesis, they scanned the brains of subjects as they made a series of different hypothetical intertemporal choices. Critically, they split the trials into two types – those where both rewards were delayed in the future, and those where the small reward could be received immediately following the experiment.

When they compared these two conditions in their analysis they found that whereas lateral PFC (dorsal and ventral) and intraparietal regions were similarly active across all trial types, limbic

structures including the VS (NAc), mPFC, posterior cingulate, and medial OFC (regions they defined as beta regions) were preferentially activated in response to choices where there was an option for immediate reward. Furthermore, when they analyzed all the choices where there was an immediate component, they could predict the choice outcome – a greater activation of limbic areas led to choice of the immediate small reward, whereas choice of the delayed reward followed a greater activation of the lateral PFC areas relative to the limbic ones. However, the hypothesis that the limbic system mediates impulsivity by its preference for immediate rewards is difficult to reconcile with animal work indicating that the integrity of the NAc and OFC is crucial for self-control and the ability to choose delayed rewards (Cardinal et al., 2004). In McClure et al.'s (2004) account, NAc or OFC lesions should, in theory, promote delayed choice as long as the DLPFC is left intact.

Kable and Glimcher (2007) have argued that McClure et al.'s (2004) study provided insufficient evidence for a dual valuation system since they did not demonstrate activity corresponding to different discount rates in the limbic and lateral PFC regions, and critically, that the discount rate in the beta regions was greater than the observed behavioral discount rate of the subjects. Without such evidence the results of their analysis could simply be explained by proposing that limbic regions track the subjective value of rewards at all delays and this preferential activity simply reflects the fact that sooner rewards are more valuable than later rewards. Thus, to explicitly determine the neural correlates of subjective value in intertemporal choice Kable and Glimcher employed a model-based approach in their analyses. They scanned participants while they were deciding between a constant smaller-sooner option and a variable larger-later option. The crux of their analysis was regressing the BOLD response against the hyperbolically discounted values of the larger-later option, derived from the choices each subject made, by estimating individuals' discount rate parameter (k) according to Mazur's (1987) hyperbolic discounting function (Eq. 2.3). These regressors identified a network of three regions which correlated with the subjective discounted value of the delayed reward – the VS, medial prefrontal cortex, and posterior cingulate cortex. This network did not exclusively value immediate rewards, as hypothesized by McClure et al. (2004) but tracked the subjective value of rewards at all delays, leading Kable and Glimcher to conclude that there is a single valuation system for delayed rewards.

Kable and Glimcher (2007) along with subsequent studies (Peters and Buchel, 2010; Prevost et al., 2010) successfully established a neural correlate of the subjective value of delayed rewards under the assumption of a single valuation process, but did not attempt to tease apart the putative subcomponents of this process. Therefore, their data cannot distinguish between a single valuation system in Green and Myerson's (2004) model and the multiplicative model in Eq. 2.5. To examine the architecture of valuation in more detail Pine et al. (2009) scanned participants while they were deciding between serially presented options that differed in both monetary amount and delay. Here the BOLD responses during the presentation of each option were modeled with the three key subcomponents U, D, and V, derived from subjects' choices according to Eq. 2.5. To ensure that no brain activity could be misattributed to a particular regressor by virtue of correlation with another, these regressors were orthogonalized. Pine et al. found that U correlated with activity in ventral tegmental area (VTA), striatum, and anterior cingulate cortex (ACC); D with VTA, striatum, insula, posterior cingulate cortex, inferior frontal gyrus, and vmPFC; and V with dorsal striatum and subgenual ACC/vmPFC. Interestingly, there was one anatomical region in the dorsal striatum where all three independent correlations overlapped, that is this area correlated independently with the discount factor, utility, and subjective value.

These results demonstrated that the brain evaluates delayed rewards in an integrative fashion. They suggest that the determinants of value are estimated separately, both with a system which relates instantaneous, undiscounted subjective value to the magnitude dimension, and with a system which calculates a discount factor to evaluate the subjective value of rewards based on their delay. Finally, a further set of regions encodes the multiplicatively integrated value of these subcomponents, which is then used to guide decisions. It was demonstrated that the dorsal striatum is the site where information from the individual value systems is integrated, because only this region represented all three subcomponents. Pine et al. (2009) thus replicated Kable and Glimcher's (2007) findings of subjective value coding in the striatum and medial PFC, but extended them to demonstrate an expanded network of regions involved in discrete aspects of the multiplicative valuation process. To illustrate the difference consider the possibility that the activity in the posterior cingulate cortex reported by Kable and Glimcher expresses the discount factor rather than overall subjective value (i.e. implicating this region solely in discounting) – a possibility supported by Pine et al.'s findings that this region only correlated with D, and not V. These results are thus consistent with the separation of D and U (Eq. 2), and support the Prelec and Loewenstein (1991) framework over the notion of a single valuation process.

Working on a similar premise, over a number of experiments, Roesch et al. (2007), Roesch and Bryden (2011) recorded from single units in rats as they made intertemporal choices. They manipulated magnitude and delay over different blocks in order to understand how these two determinants of value are represented and integrated in various brain regions. They found that activity in the majority of the OFC neurons they recorded declined as the delay to the reward increased, implicating this region in the temporal discounting of rewards. This activity also correlated with a decreased tendency for rats to choose the larger-later option trials. Interestingly, Roesch et al. (2007) argue that the OFC does not represent V and that the OFC is not a site of "common value currency" because neurons that encoded delay did not also encode reward magnitude (a requirement if they encoded discounted value). These results conflict with other electrophysiological findings, which observed delay-discounted values of reward in single neurons in pigeon OFC analog (Kalenscher et al., 2005) and in primate OFC (Roesch and Olson, 2005). Additionally, they seem to contradict the finding that OFC lesions in rats influence both temporal discount rates and sensitivity to reward (D and U, Kheramin et al., 2002, 2003, 2004). Taken together, it is not yet clear whether the animal medial PFC represents U, D, and V separately or in an integrated fashion.

Of all the single neurons recorded in rodents by Roesch and Bryden (2011) only dopamine neurons in the midbrain, especially in VTA, appeared to integrate magnitude and delay in that they encoded to both variables and their responses to the two variables were highly correlated. As a population, neurons in VS also encoded both delay and magnitude (see also forced choice voltametry data in Day et al., 2011), and some neurons did responded to both variables in a correlated manner, but overall the correlation between the response of single cells to these two variables was low. Kobayashi and Schultz (2008) demonstrated more specifically that the activity of midbrain dopamine neurons in primates tracks the discounted value of rewards in accordance with a hyperbolic discount function. Neural firing in response to Pavlovian conditioned stimuli that predicted rewards of differing delays decreased with longer delays, at a rate similar to the discount rate measured when the same animal performed a separate choice task, and followed a pattern akin to a hyperbolic decline. These neurons were also responsive to the magnitude of the predicted reward. The site of integration Pine et al. (2009) localized in the striatum may therefore reflect the output of midbrain dopamine neurons in the rodent electrophysiological recordings (Logothetis et al., 2001). Alternatively, Pine et al.'s findings could be related to coding of temporally discounted rewards in the primate dorsal striatum reported by Cai et al. (2011).

In summary, animal and human work converge on a network comprising VTA, striatum, and medial PFC which is involved in computing and representing subjective value, but the exact role of each of these regions in constructing value remains debated. Evidence from animal single unit recordings corroborates the hierarchical model of separate encoding of *D* and *U* with an integration of the two to inform subjective value, but there is a controversy as to how downstream one has to record to locate the site of this integration. In human fMRI studies, by contrast, correlates of subjective value derived from hyperbolic discount functions are fairly consistent, but only one paper so far has investigated each component of the multiplicative model individually to delineate regions implementing separate valuation functions for delay and magnitude and their integration.

EVIDENCE FOR SEPARATE REPRESENTATIONS OF *P* AND *U*

As with temporal discounting, a burgeoning human neuroimaging literature has shed a great deal of light on the neurobiological mechanisms of valuation and decision-making under uncertainty. Early studies examined BOLD responses to anticipation versus outcome of probabilistic rewards of varying magnitude (Breiter et al., 2001; Knutson et al., 2001a,b). Subsequent studies have identified the neural regions performing computations relating to the subjective value of risky prospects based on their expected values – correlates of which have been observed in the striatum and OFC (Preuschoff et al., 2006; Rolls et al., 2007; Tobler et al., 2007). The utility and probability functions which are multiplied to calculate subjective value are typically assumed to be linear and their neural correlates have also been examined individually (Knutson et al., 2001a examined magnitude and Abler et al., 2006 examined probability). In addition, more sophisticated Prospect theory-like utility and probability functions have been associated with BOLD signal in the striatum and vmPFC when participants decide between gambles (Tom et al., 2007; Hsu et al., 2009). Another school of thought proposes that in addition to expected values/utilities, the "riskiness" of probabilistic rewards is encoded by the brain and has some role in valuation. Such properties can be modeled by statistical moments such as their mathematical variance and skewness. Correlates of the former have been found in the lateral OFC, insula, and striatum (Dreher et al., 2006; Preuschoff et al., 2006, 2008; Rolls et al., 2007; Tobler et al., 2007; for detailed reviews see Rangel et al., 2008; Schultz et al., 2008).

Surprisingly however, to our knowledge only one study has attempted to tease apart the three components of the model in Eq. 1 within the same task. Tobler et al. (2007) presented their participants with stimuli predictive of outcomes which varied in their probability and magnitude. The value of each cue was computed as the product of the given, objective probability of the associated outcomes and their utility, which was modeled simply as a linear function of magnitude. They found that both the magnitude and probability of the predicted outcome correlated positively with separate regions in the striatum (dorsal and ventral respectively; **Figure 4**). In contrast, the medial PFC was only responsive to the probability of each reward. When correlating the expected value of each option predicted by the cue, Tobler et al. (2007) observed a third and separate region in the striatum. Critically, this region also overlapped with the individual probability and magnitude sensitive regions (**Figure 4**), strongly suggesting the striatum a site for the integration of probability and utility. To make the case more convincing Tobler et al. (2007) also showed that the striatal BOLD response to a particular expected value was the same whether the value was a product of a large magnitude and low probability (e.g., 200 points with a 10% probability) or vice versa (e.g., 20 points with a 100% probability). In a prior study (Fiorillo et al., 2003) the

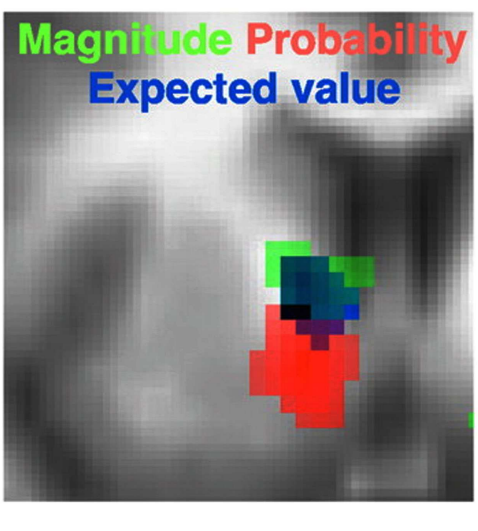

FIGURE 4 | Separate and partially overlapping striatal regions encoding unique valuation components of probabilistic rewards. Activity in dorsal striatum positively correlated with *U* (in this case magnitude), and in ventral striatum with probability. Their product, that is expected utility, positively correlated with a third, and overlapping striatal region. Figure adapted from Tobler et al. (2007).

same group showed that VTA neurons exhibited similar characteristics, correlating positively with probability, magnitude, and their multiplicative integration. Tobler et al.'s results are analogous to those of Pine et al. in the intertemporal sphere, in that both studies revealed that each component of the integrative model in Eq. 2 was represented separately in the brain. The findings of Tobler, Fiorillo, Pine, and their colleagues therefore support the multiplicative integration of separable value components rather than a single valuation function, as in the model advocated by Green and Myerson (2004).

Berns and Bell (2012) recently utilized a task where information about the probability and magnitude of rewards were presented sequentially. Although they did not look for correlates of expected value they did assess probability and magnitude independently and showed that whereas magnitude correlated with the ventral striatum BOLD responses, probability correlated with dorsal striatum activity. In this instance however the two regions did not overlap. This led the authors to conclude that although magnitude and probability are processed by distinct neural systems, their integration is not achieved by any of the models discussed above. We note, however, that none of the studies discussed in this section fully embraced the model in Eq. 1 in that they all used objective magnitudes and probabilities instead of their transformation by the utility and the probability weighting functions. This is more of a concern for null results which could be more easily explained by parameter misspecification. Therefore, before accepting Berns and Bell's conclusion it would be necessary to check whether an overlap could be found when BOLD signal is regressed against participant-specific, behaviorally derived utilities, and subjective probabilities.

EVIDENCE FOR SEPARATE REPRESENTATIONS OF *D* AND *P*

Both Tobler et al. (2007) and Pine et al. (2009) found that magnitude correlated predominantly with the striatum, whereas the modulators of magnitude – delay and risk – were expressed in the striatum and vmPFC among other regions. In both studies the striatum was considered the critical site of value integration. This begs the question of whether probability and delay share neural mechanisms, and even whether all modulators of reward are integrated in the striatum.

In support of the dissociation between D and P, Simon et al. (2009) observed poor correlation between the two across individuals. They allowed rats to choose between a safe small reward and a larger reward that was associated with varied probability of an electric shock. As expected, increasing magnitude and probability of shock biased rats to prefer the safe reward, and individual animals showed a stable pattern of responding across training sessions. The same rats also took part in probability discounting and delay discounting tasks that entailed choice between rewards without risk of shock. The sensitivity of individual animals to the risk of shock – namely, their tendency to opt for the safe reward in the main task – was correlated with sensitivity to risk in the probability discounting task but not with sensitivity to delay in the delay discounting task.

Relatively few fMRI studies have studied probabilistic and intertemporal choices in the same task (Luhmann et al., 2008; Ballard and Knutson, 2009; Peters and Buchel, 2009). Of these, only Peters and Buchel employed a model-based approach. They scanned participants while they were deciding between an immediate-small and larger-later rewards, and separately, between a certain-small and larger-probabilistic rewards. Decisions were modeled using hyperbolic discount functions to infer participant-specific parameters for k and h, which were subsequently used to calculate the subjective value of the dynamic (larger-later, larger-risky) options. Utility was modeled as a linear function of reward magnitude. To demonstrate that subjective value here was equivalent across choice types participants also performed a separate behavioral experiment where they decided between delayed and risky rewards. Indeed, Peters and Buchel found that their participants were indifferent between delayed and probabilistic rewards which had the same subjective value as calculated from the separate tasks, indicating the rewards had comparable intrinsic values. Analyses of the BOLD response revealed both overlapping and diverging activations. Whereas overlapping regions in the striatum and OFC were correlated with subjective value in both cases, other regions correlated with the subjective value of either risk- or delay-discounted reward. The authors concluded that the striatum and OFC are domain-general valuation regions which integrate results from domain specific subjective valuation systems into a common "neural currency" of value – that is a metric of value which can be used to compare the utilities of various multi-attribute options.

Though this is certainly a feasible interpretation, it is somewhat unintuitive to assume an integration of different subjective values (Vs) rather than an integration of different sub-components of a common subjective value (such as U, D, and P). Indeed, the analysis performed by Peters and Buchel (2009) does not eliminate the possibility that some of the regions identified as correlating with V could in fact have a more specific role in the representation of one of the subcomponents of subjective value[1]. Had they have compared brain activity which could only be explained by utility, the discount factors D and P (rather than inverse delay and probability), and subjective value we would have a clearer picture of the relationship between each domain specific discount system, if they are common or separable, and where and they are integrated with utility to calculate subjective value.

A critical experiment to elucidate integration across reward and its modulators, delay and probability, would be to examine the BOLD correlates when participants decide between options with all three attributes, i.e., delayed probabilistic rewards. Modeling such choices will enable a neurobiological evaluation of the multiplicative $V = U \times D \times P$ approach outlined in Eq. 2.5.

USING NEUROBIOLOGICAL EVIDENCE TO DECIDE BETWEEN ADDITIVE AND INTERACTIVE VALUATION MODELS

The claim that animals and humans represent a mixed outcome with a single value, and that this value is intimately tied to subsequent choice, is dominant in neuroeconomics and fundamental for

[1] Peters and Buchel included magnitude (m), probability (p) and the inverse of delay ($1/d$) as regressors in their model. These regressors were orthogonalised with respect to the regressor that coded value (V). Crucially, because m, d and p would, to some extent, be correlated with V, and because the analysis model ensured that V was assigned all variance that correlated with it, it is difficult to ascertain which of the regions that seemingly coded V actually coded m, d or P. This perspective may explain why the authors obtained a different map of activation when they reversed the order of orthogonalization

the models we discussed here (although it is not without its critics: Vlaev et al., 2011). Neurobiological data can provide converging evidence for this claim by showing that single cells, populations, or brain regions represent reward and other costs together. In a second step the form of neural integration could be determined. As discussed in Section "Using Neurobiological Evidence to Decide between Models of Risk and Delay" the influence of risk and delay on reward has been described in detail, and great strides have been made in our understanding of the neurobiological underpinnings of this process. We know relatively little, however, about how rewards are integrated with other costs.

We begin with a brief review of the regions thought to be involved in this process when outcomes involve a mix of rewarding food and physical effort. The dopamine system and the nucleus accumbens (NAc) are central to animals' motivation to overcome effort in order to obtain a larger reward (Phillips et al., 2007; Salamone et al., 2007; Floresco et al., 2008a,b). Dopamine antagonists and lesions of the NAc decrease the probability that high-reward/high effort options are chosen, while dopamine agonists make this choice more likely (Cousins and Salamone, 1994; Bardgett et al., 2009; Ghods-Sharifi and Floresco, 2010; Mai et al., 2012). Although exerting effort often takes time and therefore delays reward delivery, there is evidence that the dopamine system and the NAc are important for overcoming effort even when the delay to reward is controlled (Floresco et al., 2008b; Ghods-Sharifi and Floresco, 2010). For example, Day et al. (2011) used voltametry to show that in forced choice trials NAc dopamine release expressed the discounted reward value of future outcomes associated with either effort or delay. When food reward was associated with low effort or delivered immediately, dopamine release was higher than when the same amount of food was associated with high effort or delivered after a longer delay. One difficulty in interpreting these results was that exerting effort inevitably resulted in a time delay between the cue and reward delivery. However, because dopamine release was significantly lower in the high effort relative to the long delay trials the authors could conclude that the attenuation of dopamine release in high effort trials was not solely due to the time delay associated with the effort cost. The role of dopamine is not limited to physical effort but also extends to cognitive effort (Cocker et al., 2012).

The NAc is part of a network of inter-connected regions that play a role in effort-based decision-making which includes the ACC (Walton et al., 2002, 2003; Schweimer and Hauber, 2005; Rudebeck et al., 2006) and basolateral amygdala (Floresco and Ghods-Sharifi, 2007; Ghods-Sharifi et al., 2009). Animals can overcome the effects of ACC lesions with additional training (Rudebeck et al., 2006) or when the ratio between the easy-smaller and the harder-larger rewards increases (Walton et al., 2002), and ACC lesions do not always alter effort-based choices (Schweimer and Hauber, 2005), suggesting that it plays less of a key role than the NAc (Floresco et al., 2008a).

In line with this animal work, Talmi et al. (2009) and Park et al. (2011) found that a medial PFC region extending from the subgenual/perigenual ACC to vmPFC/OFC expressed the bilinear interaction between reward and pain cost at the time of decision (Eq. 6). Talmi et al. (2009) showed that activation in the subgenual ACC that was parametrically modulated by monetary reward was attenuated when the rewarding outcome also involved pain (**Figure 5**). Park et al. (2011) replicated these results, demonstrating that pain-discounted values in this region fitted the bilinear model (Eq. 6) better than the additive model (Eq. 1), and even more so when the utility function in Eq. 6 was modeled as a power function. Talmi et al. also observed the same pattern in VS, in the region of the NAc. Park et al. did not find such activation in the VS but reported increased connectivity between the subgenual ACC and the amygdala when outcomes involved high compared to low pain. Notably, the VS and amygdala regions reported by these authors were only 13 mm apart. In summary, these two datasets suggest that the vmPFC and possibly the VS and amygdala express the modulation of reward by pain costs. The convergence on these regions is not surprising given their ubiquitous role in representing subjective value across a variety of paradigms (Levy and Glimcher, 2012). Rather, these studies are important because of their computational approach, which allowed them to demonstrate that neural signals in these regions conformed better to an interactive than an additive valuation of mixed outcomes.

Hare et al. (2008) pointed out that decision values often correlate with the utility of reward $U(m)$ and with reward prediction errors, and optimized their task to decorrelate these three factors. They observed that the ACC/vmPFC region close to the regions where decision value was expressed in the studies of Talmi et al. (2009) and Park et al. (2011) expressed $U(m)$, not V, casting some doubt on the interpretation of the above findings. This concern is addressed, however, by the pattern of results in Talmi et al.'s study. In that study pain costs significantly interacted with reward value in both ventral ACC and VS, suggesting that this signal does not merely express reward utility.

Amemori and Graybiel (2012) report results that seem at first glance to challenge the bilinear model (Eq. 6). They recorded from pregenual ACC (close to the region that expressed the bilinear interaction in Talmi et al., 2009) when monkeys decided between accepting a minimum amount of food ("avoidance" decisions) and a reward that was paired with an aversive air puff ("approach" decisions). Both food amount and the strength of the air puff were manipulated parametrically. The additive model (Eq. 1) fitted behavioral choice best, better than the interactive model (Eq. 6) and more complex second and third order models.

An additional result from the same study, however, suggests that an additive model may not tell the whole story. Neuronal activity in pregenual ACC when monkeys anticipated mixed outcomes correlated with subjective value, computed according to the winning additive model, with one population of neurons coding V positively and the other negatively. Those positive-coding and negative-coding neural populations were, for the most part, evenly intermixed within the recording area, but a subzone in the ventral bank of the cingulate sulcus had a higher concentration of negatively coding neurons. Microstimulation of this subzone increased avoidance behavior, biasing monkeys to forego the mixed outcome (large reward and air puff) in favor of smaller rewards. The authors plotted cost as a function of reward, noting the decision boundary – the mixture of costs and benefits that resulted in indifference. Trials where the stimulation was "on" had shallower indifference function slopes than trials where

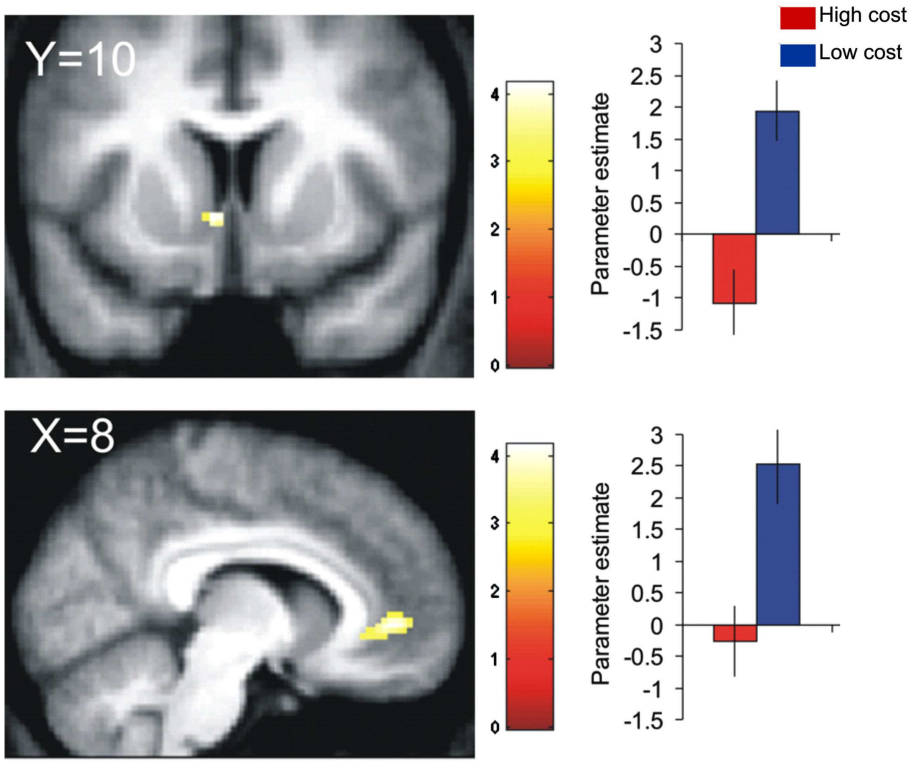

FIGURE 5 | Neurobiological evidence for the bilinear model. BOLD signal in the ventral striatum (top) and subgenual cingulate gyrus (bottom) covaried positively with reward in the low-cost conditions (blue), in which participants decided between mixtures of money and mild electric stimulation. This correlation was attenuated in the high-cost condition (red), in which participants decided between mixtures of money and painful electric stimulation. Figure adapted from Talmi et al. (2009).

the stimulation was "off," indicating reduced sensitivity to reward under stimulation. The anxiolitic drug diazepam abolished this effect of the stimulation.

To interpret these more complex data it may be helpful to consider the individual differences in Talmi et al.'s (2009) dataset. Only about half of their participants exhibited shallower reward sensitivity under pain; the other participants appeared to decide according to an additive model. The former participants, those who exhibited the interaction, likely experienced the pain cost as more threatening, because their SCR responses to pain were higher and they activated the anterior insula – a region associated with the emotional response to pain (Craig, 2003) – more strongly than those whose reward sensitivity did not change. We speculate that microstimulation in Amemori and Graybiel (2012) may have similarly rendered the aversive air puff more threatening for the monkeys, resulting in attenuated reward sensitivity.

A different map of activation altogether was obtained by Prevost et al. (2010). They used an elegant design where delay and effort costs were manipulated as closely as possible using identical trial structures. Subjective value for mixtures of reward and delay or effort was computed according to the hyperbolic model (Eq. 4). Attesting to the effectiveness of their paradigm, their delay data localized subjective value to the VS and vmPFC, replicating commonalities across many previous studies (Levy and Glimcher, 2012), and closely resembling those of another dataset which also employed the same hyperbolic model to model delay-discounted reward (Peters and Buchel, 2010). This makes the dissociation they observed between the representation of subjective value in the delay and the effort condition particularly striking. Prevost et al. reported that effort-discounted value negatively correlated with signal in the dorsal ACC and anterior insula. Signals in these regions increased when outcomes were more effortful and subjectively less valuable.

Croxson et al. (2009) have similarly observed an interaction between effort and reward in the dorsal ACC. Their task employed a forced choice paradigm, allowing a clear distinction between valuation *per se* and decision-making. They were interested in the location of BOLD responses associated with the subjective value of cues that signaled mixtures of reward and effort. The subjective value was modeled according to a variant of the trade-off model in Eq. 3, and correlated with activity in the dorsal ACC, striatum, and midbrain; yet only the dorsal ACC expressed the interaction of effort and reward, while dopaminergic midbrain and VS expressed both reward and effort but not their interaction. The difficulty in relating Prevost et al.'s and Croxson et al.'s datasets to each other is that although both studies observed an interaction between reward and effort in the same region of the ACC, the correlation between that signal and subjective value was negative in the former and positive in the latter study. By contrast, the correlation between

that signal and the level of effort required in each trial was positive in the former and negative in the latter study.

While effort is often associated with activation in the ACC, animal data provides less evidence for effort representation in the insula (Floresco et al., 2008a). Yet a relationship between insula activation and value, in the same direction as that reported by Prevost et al., was also observed in two recent studies. Brooks et al. (2010) required participants to decide between a standard delivery of 10 painful shocks and a gamble, in which either more than 10 or less than 10 shocks could be delivered in equal probabilities. As in Prevost et al. (2010) Brooks et al. also reported negative correlations between subjective gamble values and activation in the dorsal ACC and insula. In keeping with the dominant pattern in the literature, however, they also observed a positive correlation between subjective value and activity in VS. In the second study, a PET study with [18F] fallypride and D-amphetamine challenge, individual differences in dopamine function in the bilateral insula were correlated with their tendency to choose to spend more time and exert more effort in order to win larger rewards (Treadway et al., 2012). Participants who were willing to spend more time and effort for larger rewards – those who presumably evaluated this choice to have a higher subjective value than other participants – exhibited reduced dopamine function in the insula. At the same time, in line with the prevalent pattern in the literature, dopamine function in the striatum and vmPFC correlated positively with this individual difference.

The negative correlation of the insula signal with reward in Treadway et al. (2012), Brooks et al. (2010), and Prevost et al. (2010) may be related to the salience of the more effortful trials. Participants in Prevost et al.'s study may have perceived effort but not delay costs to be salient; the more effortful and time-consuming options were also likely more salient to those of Treadway et al.'s participants who chose them only infrequently, and high probability of receiving more painful shocks could also have been more salient. The "salience network" (Seeley et al., 2007), intriguingly, is identified with conjoint activation in the very same regions, dorsal ACC and bilateral insula, observed by Prevost, Brooks, and their colleagues. This reverse-inference does not, however, explain why effort-discounted value in Prevost et al.'s study did not activate the VS and vmPFC, as delay-discounted value did.

Clearly, even if the hyperbolic model does account both for the effect of effort on decision value and for the effect of delay on these values, it does not necessitate that the two share a neurobiological mechanism. A well-known set of studies demonstrated that Marmosets were willing to wait longer than Tamarins for a larger food reward, but preferred a food reward that was closer in distance to food reward that was further from them in spatial distance (Stevens et al., 2005). Because all animals grew up in captivity with limited exposure to predators, the most likely interpretation for the discounting, in Marmosets, of spatially distant food rewards was the energetic cost (effort) involved in obtaining that reward, rather than risk of predation. The double dissociation may suggest separable mechanisms for effort and delay discounting, or it could indicate differences in valuing these two costs upstream to the decision-making process, as per the discussion of D and U in Section "Evidence for Separate Representations of D and U."

The direction of the correlation between outcome mixtures and VS activity is also not without controversy. On the one hand, Kurniawan et al. (2010) also reported positive value coding in VS for mixtures of reward and effort. Although behaviorally, effort and reward did not interact significantly, the fMRI data suggested a neurobiological interaction. NAc activity was positively correlated with reward magnitude, a correlation that was only significant when participants chose to expend effort for large rewards, but not when they chose to expend effort for smaller rewards or when they chose the low-reward, low effort option. On the other hand, Botvinick et al. (2009) observed stronger NAc activation when a cue signaled a more effortful task. One possibility is that because participants were not offered any reward in that study, the direction of value coding in the VS may have reversed; but in Brooks et al. (2010) the choices were also between "bad" and "worse," and VS activity correlated positively with reward. Interestingly, Botvinick and colleagues interpreted their data according to Kivetz' model (Eq. 5), suggesting that NAc activation signals the obligatory shift of the reference point of the utility function to the right in effortful blocks.

We have reviewed neurobiological evidence that accords with interactive models of valuation, however the additive model dominates the human imaging literature. To take just one example from a particularly elegant study, Hare et al. (2008) used an additive model (Eq. 1) to compute the decision value, which in their study was the difference between the true value of a food item, established according to the elicited "willingness to pay" for that item in a Becker–DeGroot–Marschak (BDM) auction procedure, and the price at which the food item was offered to the participant. Hare et al. optimized their task to decorrelate this decision value from $U(m)$ and a reward prediction error signal, and observed a positive correlation between central OFC activity and this decision value (see also Plassmann et al., 2007). Similarly to studies that used only one model to fit their data, or compared the fit only between two models, this converging evidence for the additive model of valuation cannot rule out the possibility that an interaction term would have improved the fit.

In summary, computationally inspired studies of decision valuation, in participants deliberating between mixed outcomes, have produced converging evidence for additive as well as interactive models when correlating the value computed according to these models with neural activity. However, since most neuroimaging studies compare two models at most, it is possible that more convergence could be achieved by greater employment of model comparison.

CONCLUSION

The goal of much neurobiological work on valuation is to understand internal reward representations, namely, how the brain represents costs and benefits that are present in the environment (Dayan, 2012). Here we asked how the subjective value of outcomes is established when they consist of mixtures of costs and benefits. This is a surprisingly under-researched topic despite a large empirical and computational body of work on decision-making.

The way people value costs and benefits, individually, has been studied extensively. Here we reviewed current thinking and empirical data concerning the subjective value of monetary gains and losses, and the influence of risk and time delay on this value. We discussed data that support and challenge available models, and the potential for neurobiological work to illuminate some open questions. By comparison, the functional form of cost-benefit analysis – the decision between mixtures of rewards and costs – is relatively unknown. We described two general classes of models – additive and interactive – for the process of integrating rewards and costs into a single decision value. The economic literature typically assumes that costs and benefits are integrated additively, but there is also support for a variety of interactive models. Yet only a handful of studies directly compare additive and interactive models, or between interactive model variants. Modeling-informed empirical work is clearly necessary in order to enhance understanding of the neurobiological mechanism that allows animals and humans to integrate costs and benefits. Empirical work on this intriguing question should proceed with caution; not assuming that integrated representations of the subjective value of anticipated outcomes are natural kinds, but to demonstrate their existence empirically (Vlaev et al., 2011). We hope that by clarifying some of the main candidates for valuation, and the way neurobiological data can support or challenge them, we will encourage further empirical work on the mechanism that allows animals and humans to decide optimally in a complex environment.

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APPENDIX

Phillips et al. (2007) suggested that when a participant is faced with a choice of taking or foregoing an action which would yield both rewards M_R and costs M_C, the value of the action can be expressed as the value $V(M_R, M_C)$ relative to the value of the same action if cost was not involved, $V(M_R, M_C = 0)$. When there are no costs the value is maximal because $V(M_R, M_C) = V(M_R, M_C = 0)$.

They observed that there is a specific cost C_i which translates to $V(M_R, M_C) = 0$, namely, lead the participant to be indifferent about the choice. When $M_C = C_i$ participants are not motivated either to act or avoid acting; consequently, they act 50% of the time. Costs higher than C_i mean that $V(M_R,M_C) < 0$ and bias the participant against the action; costs lower than C_i mean that $V(M_R,M_C) > 0$ and favor taking the action. The authors note that there is limited evidence as to the exact functional forms of the indifference function C_i and offered a tentative, plausible form in their **Figure 1**, where cost is a linear function of dopamine:

$$M_C = a_1 \times \mathrm{DA} \tag{A1}$$

With the constant $a_1 > 0$. Given evidence that dopamine level (DA) is a function of currently available reward and the maximum levels of dopamine DAmax observed in the task context, and that the utility of reward is a decelerating function of reward magnitude, DA was described according to the following function:

$$\mathrm{DA} = \mathrm{DA_{max}} \times \frac{\mathrm{M}_R}{(\mathrm{M}_R + a_2)} \tag{A2}$$

With the constant $a_2 > 0$. Therefore,

$$C_i = a_3 \times \frac{M_R}{(M_R + a_2)} \tag{A3}$$

With the constant $a_3 > 0$.

The authors further proposed a specific form for a cost-benefit function Z (**Figure 2**), which depicts the ratio of outcome with cost to the same outcome without cost.

$$Z = \frac{V(M_R, M_C)}{V(M_R, M_C = 0)}. \tag{A4}$$

Because when there is no response cost the two outcomes are equivalent (the ratio is maximal), and because when the ratio is 0.5 decision-makers are indifferent between the two outcomes, we determine that Z passes between (C_i, 0) and (0,1). Therefore

$$Z = \frac{1 - M_C}{C_i} \tag{A5}$$

The authors did not provide an explicit model for $V(M_R, M_C = 0)$, the utility of rewarding outcomes that are not accompanied by costs. On the basis of their choice of Eq. 2 to represent DA and their reasoning for that choice we selected the same form to also model reward utility:

$$V\,(M_R, M_C = 0) = R_{\max} \times \frac{M_R}{(M_R + a_4)} \tag{A6}$$

Combining the above equations provides us with a value function for mixed outcomes:

$$V\,(M_R, M_C) = \left[R_{\max} \times \frac{M_R}{(M_R + a_4)}\right] - \left[\left(\frac{R_{\max}}{a_3}\right) \times \mathrm{M}_C \times \frac{(\mathrm{M}_R + a_2)}{(\mathrm{M}_R + a_4)}\right] \tag{A7}$$

To understand its implications we considered the case where Mr $<<$ $a4$, namely when the utility of Mr, $V(M_R, M_C = 0)$, resembles a linear function. In this case, some algebra will show that

$$V(M_R, M_C) = \left(\frac{R_{\max}}{a_4}\right) \times \left(\mathrm{M_R} - \left[\left(\frac{\mathrm{a_1}}{\mathrm{A_3}}\right) \times M_C\right] - \left[\left(\mathrm{M_R} \times \frac{M_C}{a_3}\right)\left(1 - \frac{a_2}{a_4}\right)\right] - \left[\frac{R^2}{a_4} \times \left(1 - \frac{M_C}{a_3}\right)\right]\right) \tag{A8}$$

Now, as $\mathrm{M_R} << a_4$, we could probably drop the last term as it is small (it is always a positive term) and "tidy up," introducing constants x_1, x_2, and x_3':

$$V(M_R, M_C) = X_1 \times \mathrm{M_R} - X_2 \times M_C - X_3 \times \mathrm{M_R} \times M_C \tag{A9}$$

With x_3 a constant that is either positive or negative:

$$X_3 = \left(\frac{R_{\max}}{a_4}\right) \times \frac{\left(\frac{1-a_2}{a_4}\right)}{a_3} \tag{A10}$$

And x_1 and x_2 positive constants.