CHAPTER

Neural coding of computational factors affecting decision making

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Abstract

We constantly need to make decisions that can result in rewards of different amounts with different probabilities and at different timing. To characterize the neural coding of such computational factors affecting value-based decision making, we have investigated how reward information processing is influenced by parameters such as reward magnitude, probability, delay, effort, and uncertainty using either fMRI in healthy humans or intracranial recordings in patients with epilepsy. We decomposed brain signals modulated by these computational factors, showing that prediction error (PE), salient PE, and uncertainty signals are computed in partially overlapping brain circuits and that both transient and sustained uncertainty signals coexist in the brain. When investigating the neural representation of primary and secondary rewards, we found both a common brain network, including the ventromedial prefrontal cortex and ventral striatum, and a functional organization of the orbitofrontal cortex according to reward type. Moreover, separate valuation systems were engaged for delay and effort costs when deciding between options. Finally, genetic variations in dopamine-related genes influenced the response of the reward system and may contribute to individual differences in reward-seeking behavior and in predisposition to neuropsychiatric disorders.

Keywords

reward uncertainty, prediction error, subjective value, valuation systems, value-based decision making, genetic variations

1 BASIC COMPUTATIONS INVOLVED IN DECISION MAKING

We constantly need to make decisions that can result in rewards of different amounts, types, probabilities, and which occur at various delay durations. To characterize the neural coding of such computational factors affecting value-based decision making,

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it is first necessary to understand how they are coded in the brain when no choice needs to be done. This is the approach taken by our group in the past few years which focused on understanding how reward information processing is influenced by parameters such as reward magnitude, probability, or uncertainty. We have used intracranial recordings in patients with epilepsy and fMRI in healthy controls to decompose brain signals modulated by these computational factors (Caldu and Dreher, 2007; Dreher et al., 2006, 2008, 2009; Metereau and Dreher, 2012; Sescousse et al., 2010; Vanni-Mercier et al., 2009).

The focus of this chapter is to characterize how computational factors such as reward probability and reward uncertainty are coded in the human brain, how different types of rewards engage specific brain systems, how the brain assigns values to different options under consideration, how principles used in models of perceptual decision making can be extended to value-based decision making, and how polymorphisms in genes-affecting dopamine transmission modulate reward-related mechanisms.

2 MONKEY ELECTROPHYSIOLOGY: MIDBRAIN DOPAMINERGIC NEURONS AND THE COMPUTATION OF SUBJECTIVE VALUE, UNCERTAINTY, AND PREDICTION ERROR

A number of mathematical measures have recently been associated with transient and sustained aspects of dopaminergic responses (Fig. 2). These measures are based on the fact that rewards can be characterized by probability distributions of reward values. Two main parameters of probability distributions can then be defined: the expected value (the anticipated "mean," first statistical moment of the distribution) and the variance (second moment) or its square root (standard deviation). The latter measures the degree of uncertainty in known probability distributions, and entropy can also be considered as a proxy for uncertainty. In addition, it is possible to define prediction errors (PEs) as a measure of the deviations from previous reward expectations. PE can be either positive (when the reward delivered is better than expected), null (when the reward delivered is as expected), or negative (less or no reward delivered at the expected time) (Schultz et al., 1997; Sutton and Barto, 1998). PEs are used to learn the value of states of the world and are critical for learning how to make better choices in the future.

Electrophysiological studies recorded dopaminergic neurons in monkeys during classical conditioning experiments, in which an association had to be learnt between a visual predictor (conditioned stimulus) and a rewarding outcome (unconditioned stimulus). These studies indicate that dopaminergic neurons code in a transient fashion both the expected value at the time of the cue and the PE at the time of the outcome. This signal may be sent to the striatum and prefrontal cortex (PFC) to influence reward-dependent learning (Bayer et al., 2007; Schultz, 2000; Schultz and Dickinson, 2000). However, recent electrophysiological studies also indicate that dopaminergic neurons not only code the expected value and a transient reward

prediction error (RPE) signal but also a sustained signal during the delay between the cue and the potential outcome. This sustained signal is maximal with highest reward uncertainty (i.e., reward probability = 0.5) and may be functionally important for risk seeking behavior and/or exploratory behavior (Fiorillo et al., 2003; see Section 3). Together, these results suggest that dopaminergic response may reflect three types of mathematical measures: the subjective value of the reward at the time of the conditioned stimulus, the uncertainty or variance of reward information during the delay period between the conditioned stimulus and outcome, and the PE at the time of the outcome. These signals are sent to a number of neural structures involved in computing value-based signals involved in decision making.

In classical conditioning experiments, each of the factors mentioned before (magnitude, probability, timing uncertainty, and delay) influences the phasic expected value signal occurring at the time of the conditioned stimuli. That is, the phasic response of dopamine neurons to the conditioned stimuli monotonically increases with probability and magnitude (Tobler et al., 2005) and decreases with the reward delay in temporal discounting paradigms, both in Pavlovian conditioning (Kobayashi and Schultz, 2008) and in intertemporal choice (Roesch et al., 2007). Moreover, at the time of the outcome, the response of dopamine neurons increases with reward delay and magnitude, and decreases with increasing reward probability (Fiorillo et al., 2003; Kobayashi and Schultz, 2008). However, the magnitude of the transient response of dopaminergic neurons at the outcome appears to be identical for different magnitudes that are delivered with maximal uncertainty ($P = 0.5$), despite the fact that the absolute difference between actual and expected volume magnitude varied over a large range (Tobler et al., 2005).Thus, the transient responses of dopamine neurons do not appear to scale according to the absolute difference between actual and expected reward. Rather, the sensitivity of these neural responses appears to adapt according to the discrepancy in magnitude between two potential outcomes.

2.1 Human neuroimaging studies on PE

In the past 10 years, a large number of human neuroimaging studies have investigated the neural correlates of the PE signal. A number of these studies suggest that activity in the ventral striatum and the PFC correlates with PE related to stimulus–response associations or rewards of different types, such as faces, money, or juice (Abler et al., 2006; Berns et al., 2001; Bray and O'Doherty, 2007; Dreher et al., 2006; Fletcher et al., 2001; McClure et al., 2003; O'Doherty et al., 2003). When examining the influence of reward magnitude during reward anticipation and at the time of rewarded outcome, increased activity has been observed in several brain regions, particularly in the ventral striatum. For example, increased ventral striatal activation was found with increasing magnitude of anticipated gains but not losses (Knutson et al., 2001, 2005). Several studies also investigated the influence of reward probability on brain activation. Some gambling studies found that ventral striatal activity increased with reward probability (Abler et al., 2006; Preuschoff et al., 2006; Yacubian et al., 2006), while a cued reaction time study failed to find ventral striatal

activation as a function of increasing probability (Knutson et al., 2005). In some of these studies, a region of the medial PFC also showed increasing activation during anticipation of rewards with increasing probability (Knutson et al., 2005; Yacubian et al., 2006).

In a recent monetary fMRI study using slot machines varying known reward probability and magnitude, we could distinguish between transient and sustained signals using a fixed long anticipatory period (Fig. 1; Dreher et al., 2006). We found that the midbrain was activated both transiently with the PE signal and in a sustained fashion with reward uncertainty. Moreover, distinct activity dynamics were observed

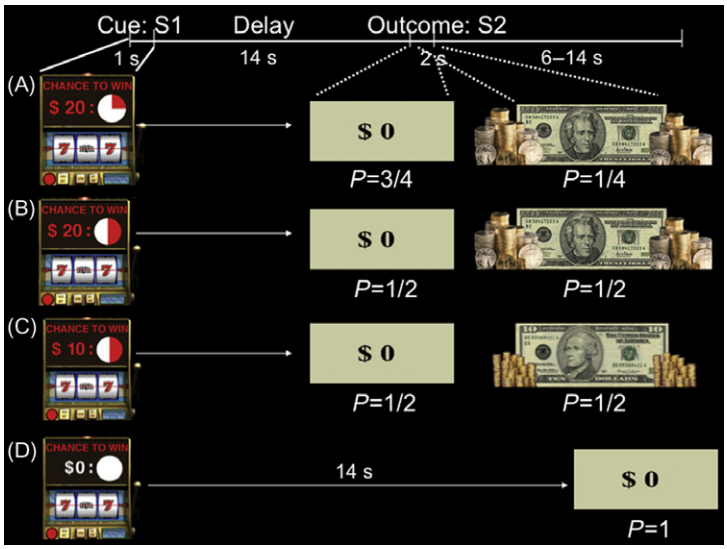

FIGURE 1

Task design of the slot machines task. Four types of "slot machines" (types A–D) were presented pseudorandomly to the subjects. The probabilities of winning different amounts of money or nothing were indicated, respectively, by the red and white portions of a pie chart above the slot machines. The slot machine and pie chart remained on the screen throughout the delay duration (as shown for slot D). Each trial consisted of a brief (1 s) presentation of the cue (stimulus S1, one of the four slot machines), followed after a fixed delay (14 s) by the outcome S2 (either $0 or a picture of a $10 or $20 bill, lasting 2 s). This long fixed delay allowed us to distinguish transient hemodynamic signals associated with the error prediction signal at S1 and S2 from the sustained signal associated with reward uncertainty during the delay. During each trial, subjects indicated which "slot machine" was presented by pressing a response button both at the cue S1 and the outcome S2 (regardless of winning or not). Reward delivery was not contingent upon subject response.

Figure taken from Dreher et al. (2006) with permission.

in postsynaptic midbrain projection sites: the PFC responded to the transient PE signal, while the ventral striatum covaried with the sustained reward uncertainty signal (Fig. 2). This sustained ventral striatum activity was confirmed by a subsequent study reporting that this brain region encodes both expected reward and risk (Preuschoff et al., 2006). The frontal network we observed both at the time of the cue and at the time of the outcome was specifically involved with the RPE signal because it was not significantly activated by reward uncertainty during the delay and was

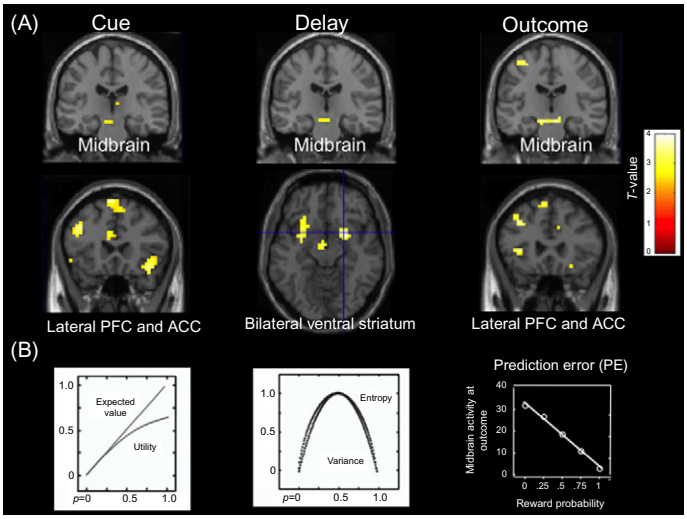

FIGURE 2

Transient and sustained modes of activities. (A) Top: Location of transient midbrain responses covarying with the error prediction signal at the cue S1 (*left*) and at the rewarded outcome S2 (*right*). Consistent with electrophysiological recordings (Fiorillo et al., 2003), the human midbrain region was transiently activated with higher reward probability at the cue S1 and with lower reward probability at the rewarded outcome S2. Moreover, the midbrain region showed higher sustained activity with reward uncertainty during the delay period (Dreher et al., 2006). Bottom: Location of transient lateral prefrontal and anterior cingulate cortices responses covarying with the error prediction signal at the cue S1 (*left*) and at the rewarded outcome S2 (*right*). Middle: Location of sustained bilateral ventral striatum activities covarying with the reward uncertainty signal during the delay period. (B) Theoretical measures associated to the three stages of the task. The expected value or utility function is coded transiently at the time of the cue, the entropy or variance is coded in a sustained fashion during the delay period between the cue and the reward, and the PE is coded transiently at the time of the outcome. Importantly, the expected value increases with reward probability and the PE decreases with reward probability, while the sustained mode of activity coding the entropy or variance varies in a highly nonlinear fashion with reward probability.

Figure adapted from Dreher et al. (2006).

significantly more activated in association with these phasically modeled responses than in association with a sustained-modeled response related to reward uncertainty during the delay period. Our results extend previous fMRI reports that the dorsolateral PFC, inferior frontal gyrus, and orbitofrontal cortex activity correlates with a PE signal related to abstract stimulus–response associations or taste reward, although some of these studies focused more on ventral striatal activity (Abler et al., 2006; Berns et al., 2001; Bray and O'Doherty, 2007; Dreher et al., 2006; Fletcher et al., 2001; McClure et al., 2003; O'Doherty et al., 2003). The lateral PFC may generate the reward prediction because neurons from this brain region represent predictions about expected rewards according to the context (Kobayashi et al., 2002; Watanabe et al., 2002).

In two subsequent fMRI studies, we investigated how PE is modulated not only by reward probability and magnitude but also by reward type (money, fruit juice, and erotic stimuli) and by reinforcement nature (reward vs. punishment). In a first study, we explicitly informed subjects on subsequent reward type (erotic stimuli or monetary reward), probability, and intensity. We found that activity in the ventral striatum not only correlated with reward magnitude for both monetary and erotic rewards, but also with RPE regardless of reward nature (primary or secondary reinforcers; Sescousse et al., 2010).

2.2 Neural coding of the salient PE in monkeys and humans

Based on a wealth of evidence from electrophysiological recording studies in nonhuman primates, rodents, and humans, it has been widely assumed that dopaminergic neurons encode an RPE, with a positive phasic response when the outcome is better than expected (unexpected reward or omission of expected punishment) and a negative response when it is worse than expected (unexpected punishment or omission of expected reward) (Schultz et al., 1997). According to this hypothesis, referred to as the RPE hypothesis, the sign of the PE is opposite for rewards and punishments.

However, in awake monkeys, recent recordings from the same dopaminergic neurons for rewards and aversive events point to the coexistence of a phasic dopaminergic signal encoding biologically salient events conveying both positive and negative information (Matsumoto and Hikosaka, 2009). During a Pavlovian procedure, one class of dopaminergic neurons located ventromedially, some in the VTA, are excited by unexpected rewards and inhibited by unexpected aversive stimuli, as expected by the RPE hypothesis. Yet, a larger subpopulation of dopamine neurons, located more dorsolaterally in the substantia nigra pars compacta, are excited both by unpredictable reward and aversive stimuli, as would predict a salient PE (SPE) hypothesis. Moreover, recent results in rodents confirm that, while some dopaminergic neurons of the VTA are inhibited by aversive stimuli, others are excited by these same stimuli (Brischoux et al., 2009). These findings suggest that different groups of dopamine neurons convey RPE and SPE signals, shedding light on increased striatal dopamine levels observed not only during appetitive conditioning (Reynolds et al., 2001) but also during aversive conditioning (Pezze and Feldon, 2004). Together,

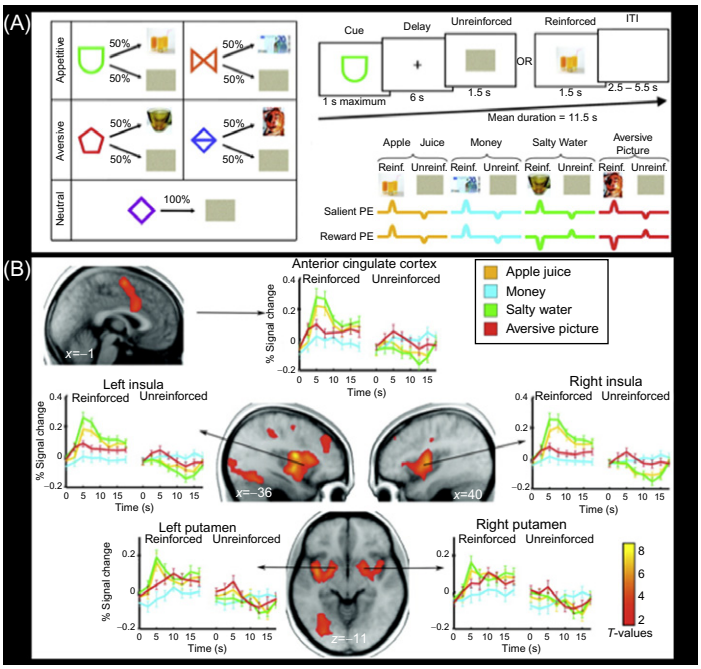

FIGURE 3

Distinguishing prediction error and salient prediction error. (A) Experimental design and computational model. Subjects learned to associate various cues with four different types of reinforcers (two appetitive and two aversive) in a classical reinforcement learning paradigm. Two types of cues were followed by positive reinforcers (apple juice and money) on 50% of occasions or by a scrambled picture (unreinforced), two other types of cues were followed by negative reinforcers (salty water and aversive picture) on 50% of occasions or by a scrambled picture (unreinforced), while some cues were always followed by a scrambled picture (neutral condition). Top right: Time course of a single trial. After the cue presentation, subjects pressed a response button, immediately followed by a delay period and by the reinforcer or by a scrambled picture. Top right (bottom): Salient computational model—predicted neural response. Schematic showing the mean representation of the SPE signal which responds to reward and punishment in the same way, as motivationally salient events, generating positive PE for reinforced trials and negative PE for unreinforced trials. Top right (bottom): Reward computational model—predicted neural response. The RPE model signals rewards and punishments in opposite ways, generating a positive PE when an unexpected reward is delivered or when an expected punition is missed and generating a negative PE when an unexpected punishment is delivered or an expected reward is missed (Unreinf., Unreinforced; Reinf., Reinforced). (B) Gustatory SPE signal. Statistical parametric maps showing that activity in ACC, bilateral putamen, and bilateral insula correlates with the SPE in the two gustatory conditions (conjunction analysis). Plotted below are the time courses of inferred mean neuronal activity aligned to the onset of the reception phase for the four types of outcomes, in each of these brain regions. Reinforced and unreinforced trials are plotted separately. Color bars represent *T* values.

Figure taken from Metereau and Dreher (2012) with permission.

these results raised the possibility of the coexistence of two brain networks active during the learning of associations between cues and rewards or punishments: a reward brain network, treating reward and punishment in opposite ways (opposite hedonic valences), and a salient brain network, which treats them in a similar manner as motivationally salient events.

In humans, it was unclear whether specific brain structures receiving afferents from dopaminergic neurons code a SPE and whether this signal depends upon reinforcer type. In a recent fMRI study, we investigated this question using temporal-difference modeling during a classical conditioning learning paradigm with both aversive and rewarding outcomes (Fig. 3; Metereau and Dreher, 2012). In this model-based functional magnetic resonance imaging study, we implemented a reinforcement learning model to compute the PE, while subjects underwent a Pavlovian conditioning procedure with two types of rewards (pleasant juice and monetary gain) and two types of punishments (aversive juice and aversive picture). Cues were associated with a 50% probability to either one of these four reinforced outcomes or to a neutral outcome (scramble picture). We tested two types of computational models. According to the SPE model, responses to reward and punishment appear in the same way as motivationally salient events, generating positive PE for reinforced trials and negative PE for unreinforced trials. In the reward PE model, rewards and punishments respond in opposite ways, generating a positive PE when an unexpected reward is delivered or when an expected punition is missed and generating a negative PE when an unexpected punishment is delivered or an expected reward is missed. The results revealed that activity of a brain network composed of the striatum, anterior insula, and ACC covaried with an SPE for appetitive and aversive juice. Moreover, amygdala activity correlated with an SPE for these two reinforcers and for aversive pictures. These results provide insights into the neurobiological mechanisms underlying the ability to learn stimuli-rewards and stimuli-punishments contingencies, by demonstrating that the network reflecting the SPE depends upon reinforcement's type (Fig. 3).

3 COMPUTATION OF UNCERTAINTY SIGNALS IN THE HUMAN BRAIN

Until recently, it was unknown whether the transient and sustained modes of midbrain activities (Fiorillo et al., 2003) could also be observed in humans and whether they could be distinguished by postsynaptic dopaminergic projection sites. Using fMRI, we have successfully distinguished transient and sustained dynamics of the dopaminergic system in healthy young humans using a new reward task based on the monkey electrophysiology study, that systematically varied monetary reward probability and magnitude in the absence of choice (Dreher et al., 2006). The results showed that the human dopaminergic midbrain exhibits similar activity dynamics as midbrain from nonhuman primates. Moreover, specific dopaminergic projection sites were activated: (a) the ventral striatum, during anticipation of rewards with

maximal uncertainty (reward probability = 0.5) and (b) the PFC and anterior cingulate cortices (ACC) at the time of the outcome, correlating with a transient PE signal coding the difference between expected and obtained rewards (Fig. 2). These results indicate that specific functional brain networks subserve the coding of sustained and transient aspects of reward information in humans. These results are important because they support a unified cross-species view in which dopaminergic neurons obey common basic principles of neural computation and provide important new insights into human reward information processing.

Our finding of two networks covarying with different reward signals may indicate that dopaminergic projection sites can distinguish between the two signals. It is also possible that these targets show independent transient (PFC) and sustained (ventral striatum) activities related to the two signals and/or that they help to shape dopaminergic neuronal activity by differentially modulating their phasic and sustained modes of firing, which occur independently in individuals neurons (Fiorillo et al., 2003). This latter hypothesis is supported by anatomical observations that different populations of dopaminergic neurons are innervated predominantly by the target areas to which they project, or by the regions that, in functional terms, are the most closely linked to the target areas (Sesack et al., 2003). For example, in rodents, dopaminergic neurons projecting to the PFC receive direct reciprocal inputs from this brain region, but not from the striatum, while dopaminergic neurons projecting to the striatum receive afferents from that brain region, but not from the PFC, thereby forming two projection systems (Sesack et al., 2003). This suggests a general principle for midbrain dopaminergic neuronal afferents regulation, the PFC, and the striatum being responsible for regulating and controlling different modes of dopaminergic neuronal firing.

Interestingly, another study involving choice behavior investigated the neural correlates of risk, modeled as outcome variance (risk being maximal at 50% probability), and found increased activation in the insula, lateral orbitofrontal cortex, and midbrain (Preuschoff et al., 2006). Insula activity also correlated with uncertainty in other paradigms involving money and nonmonetary stimuli (Grinband et al., 2006; Huettel et al., 2005).

The discrepancy between the different findings of the ventral striatum coding either PE or reward uncertainty may be due to several factors. First, most fMRI studies investigating prediction signal used temporal-difference modeling in the context of learning paradigms. In contrast, in our early monetary reward fMRI paradigm (Dreher et al., 2006), there was no learning of cue–outcome associations. So, the putamen activation we observed during anticipation with maximal uncertainty cannot be attributed to a learning effect. Second, one limitation of most fMRI studies varying reward probability is that they could not clearly separate the transient and sustained signals because the delay duration between the conditioned stimulus and the outcome was either too short or randomly jittered (which is a problem since transient dopaminergic responses are known to depend upon timing uncertainty) (Abler et al., 2006; Preuschoff et al., 2006). To address this problem, we have recently used intracranial recordings in humans to investigate the neural coding of PE and uncertainty with a more precise temporal definition (Fig. 4; Thomas and Vanni-Mercier, 2008; Vanni-Mercier et al., 2009).

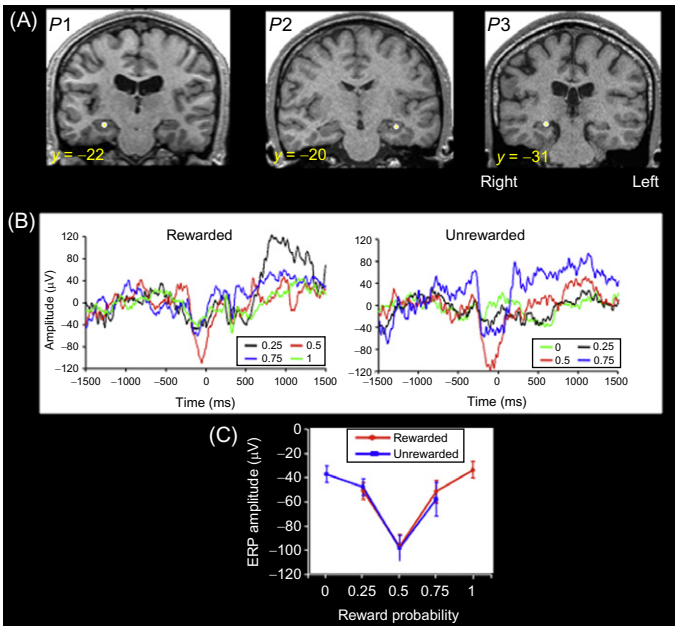

FIGURE 4

The hippocampus codes the uncertainty of cue–outcome associations. (A) Location of intracranial electrode contacts. Coronal MRI slices from the three subjects showing the location of the intracranial electrode contacts in the hippocampus. The contacts in the hippocampus yielding the largest potentials are shown in bold square. (B) Uncertainty coding in the human hippocampus. Each color line represents the mean ERPs for each slot machine ($P=0$, 0.25, 0.5, 0.75) at the outcome period. At the time the third spinner stopped (−500 to 0 ms), the subject knew whether they would win the money shown at time $t=0$. Hippocampal ERP amplitudes code uncertainty (maximal for $P=0.5$) at the outcome (−500 to 0 ms), regardless of winning or not. (C) Mean peak ERP amplitudes averaged across subjects at the outcome, as a function of reward probability, both for rewarded and for unrewarded trials.

Figure adapted from Vanni-Mercier et al. (2009) with permission.

Although hippocampal–midbrain functional interactions are well documented and the hippocampus receives reward-related information not only from midbrain dopaminergic neurons but also from other components of the reward system, such as the amygdala and orbitofrontal cortex (Suzuki and Amaral, 1994), it was still unknown whether it codes statistical properties of reward information, such as PE or reward uncertainty. To answer this question, we recorded hippocampal activity in epileptic patients implanted with depth electrodes while they learned to associate cues of slot machines with various monetary reward probabilities (P) (unlike our early fMRI monetary reward paradigm in which probability were explicitly given to the subjects) (Vanni-Mercier et al., 2009; Fig. 4). Subjects estimated the reward

probability of five types of slot machines that varied with respect to monetary reward probabilities P (0–1) and that could be discriminated by specific fractal images on top of them. Trials were self-paced and were composed of four distinct phases: (1) Slot machine presentation (S1): subjects pressed one of two response keys to estimate whether the slot machine frequently delivered 20€ or not, based on the outcomes of all the past trials; (2) delay period (1.5 s): subject's key press triggered three spinners to roll around and to successively stop every 0.5 s during 0.5 s; (3) outcome S2 (lasting 0.5 s): the third spinner stopped and revealed the trial outcome (i.e., fully informing the subject on subsequent reward or no reward delivery). Only two configurations were possible at the time the third spinner stopped: "bar, bar, seven" (no reward) or "bar, bar, bar" (rewarded trial); (4) Reward/No reward delivery (1 s): picture of 20€ bill or rectangle with 0€ written inside.

The results showed that the amplitudes of hippocampal negative event-related potentials (ERP), covaried with uncertainty at the outcome, being maximal for $P = 0.5$ and minimal for $P = 0$ and $P = 1$, regardless of winning or not (Fig. 4). This inverted U-shape relationship is typical of uncertainty coding and is incompatible with PE, novelty, or surprise coding, which would have predicted a negative monotonic correlation between ERP amplitudes and increasing reward probability (Dreher et al., 2006; Fiorillo et al., 2003). This uncertainty coding of cue–outcome associations by the hippocampus may constitute a fundamental mechanism underlying the role of this brain region in a number of functions, including attention-based learning, associative learning, probabilistic classification, and binding of stimulus elements, that until now, have received no unified explanation concerning the underlying information processing performed by the hippocampus to achieve them. We propose that the uncertainty coding of cue–outcome associations may constitute the general computational mechanism used by the hippocampus to achieve these different functions. The transient uncertainty signal emitted by the hippocampus at the outcome may play a complementary role to the sustained uncertainty signal emitted by midbrain dopaminergic neurons during the delay period between the cue and the outcome. This finding constitutes a major advance in the knowledge of the functional properties of the human hippocampus and has crucial implications for understanding the basic neural mechanisms used by the brain to extract statistical relationships from the environment. It is clear that an ubiquitous coding of uncertainty exists in the human brain, particularly in the midbrain, ventral striatum, insula, ACC, and orbitofrontal cortex (Dreher et al., 2006; Hsu et al., 2005; Preuschoff et al., 2006, 2008; Tobler et al., 2007); and the present study revealed that the hippocampus also participates to uncertainty processing. Future studies are needed to pinpoint the specific roles and time-course of each structure in computing uncertainty in different contexts.

4 SEPARATE VALUATION SYSTEMS FOR MAKING DECISIONS RELATED TO DELAY AND EFFORT COSTS

When presented with several options, we need to assign subjective values to each of them to make a choice. This valuation needs to weight available options in terms of cost and benefit (the prospect of reward) in order to select the option with the highest

subjective value. Psychological and economic studies have shown that outcome values are discounted with longer delays, an effect known as temporal discounting. A recent electrophysiological study demonstrated that when monkeys choose between sooner smaller available rewards and later larger rewards, the longer the delay of the later larger reward, the less firing of dopaminergic neurons at the time of the conditioned stimuli (Kobayashi and Schultz, 2008). Moreover, this reduction in firing rate followed a hyperbolic decay function similar to that observed in choice behavior. In addition, dopamine responses increased with longer delays at the time of the delayed larger reward delivery, interpreted as reflecting temporal uncertainty and partial learning. These fundamental results establish that dopamine responses reflect the subjective reward value discounted by delay and may provide useful inputs to neural structures involved in intertemporal choices.

Recent fMRI findings on delay-discounting support two opposite theories. According to the first set of experiments, there may be two separate systems in the brain: a limbic system computing the value of rewards delivered immediately or in the near future based on a small discount factor, and a cortical system computing the value of distant rewards based on a high discount factor (McClure et al., 2003, 2007; Schweighofer et al., 2007, 2008; Tanaka et al., 2004). Discounting would result from the interaction of these two systems associated with different value signals. According to the second theory, based on a recent fMRI study, there would be a single valuation system simply discounting future rewards (Kable and Glimcher, 2007). One way to conciliate these apparent opposite views is that the striatoprefrontal network might integrate information that is encoded elsewhere in the brain into a single value signal, but that immediate and delayed outcomes activate different types of information that are used to compute the reward value (Rangel et al., 2008). One further recent finding is that the orbitofrontal cortex may separate the representation of the temporal discount factor applied to distant rewards from the representation of the magnitude of the reward, suggesting that these quantities may be integrated elsewhere in the brain.

Standard theories of economic decision making do not distinguish between decisions related to different types of costs, such as delay or effort costs. A choice is made after a valuation stage, regardless of the nature of the cost. However, lesion studies in rodents suggest at least partial dissociations between the neural structures used to assess delay- and effort-based decision making (Floresco et al., 2008; Rudebeck et al., 2006; Walton et al., 2006). Despite the fundamental importance of these animal studies for paving the way in identifying the neural substrates involved in making decisions about delay and effort costs, it is unknown whether these circuits can be generalized to humans and whether they specifically concern the valuation stage. Indeed, specifying the roles of brain structures specifically involved during the valuation stage, and not during the subsequent waiting/effort periods, has proved difficult because animal studies cannot pinpoint exactly at what point in the decision-making process a lesioned animal is impaired. Yet, a number of them have shown that it is neither the ability to wait nor the exertion of effort *per se* that is impaired by the use of control conditions (Rudebeck et al., 2006).

Although a few neuroimaging studies started to shed some light on the neural substrates involved in processing subjective value during delay discounting, virtually nothing is known about how effort is discounted in humans. Animal studies demonstrated that the ACC, the ventral striatum, and the orbitofrontal cortex make specific contributions to decision when costly options involve an effort or a delay (Rushworth et al., 2007; Walton et al., 2006). However, in humans, it is unclear whether there are dissociable pathways underlying different types of costs such as effort and delay to reward.

In order to answer this question, we designed a delay/effort-discounting task involving primary rewards (visual erotic stimuli) (Prevost et al., 2010). Heterosexual men were scanned in an event-related fMRI paradigm while performing the task (Fig. 5). On every trial, an incentive cue (fuzzy pictures of naked women) briefly appeared on a screen and was followed by the instruction (delay or effort), together with a thermometer indicating the level of delay or effort. Depending on the incentive cue and the proposed cost level, subjects decided whether to invest in the proposed effort (to tolerate the proposed delay) to view the erotic image in clear for 3 s or to perform a minimal effort (to wait for only 1.5 s) to view it for 1 s only. Then, subjects either waited passively in the delay condition (range: 1.5–9 s) or squeezed a hand-grip in the effort condition. We found that choices of the costly option depended upon the subjective value of incentive cues, as indexed by postscan ratings of these cues, and upon the required level of delay and effort.

We found that humans devalue rewards associated with physical effort in a strikingly similar fashion to those they devalue that are associated with delays, and that a single computational model derived from economics theory can account for the behavior observed in both delay discounting and effort discounting (Fig. 6). However, our neuroimaging data revealed that the human brain uses distinct valuation subsystems for different types of costs, reflecting in opposite fashion-delayed reward and future energetic expenses. The ventral striatum and the ventromedial PFC represent the increasing subjective value of delayed rewards (Fig. 6), whereas a distinct network, composed of the ACC and the anterior insula, represents the decreasing value of the effortful option, coding the expected expense of energy (Fig. 6).

To test whether the brain networks identified with subjective valuation of delay and devaluation of effort engage separate neural systems, we also performed direct comparisons of the activities of brain regions in which the positive correlation with subjective value of the delayed reward was significantly greater (respectively lower) than the negative correlation with subjective value of the effortful reward. These direct whole-brain statistical comparisons of the effects of subjective value in the effort and delay conditions, as well as ROI comparisons between beta estimates, demonstrated the specificity of the brain networks identified in the valuation of delayed reward and in the devaluation of effortful reward.

The ventral striatum, the ACC, and the vmPFC are strongly implicated in cost/benefit decision making. Yet, their relative roles have never been directly simultaneously compared using a similar design for decisions concerning delay and effort costs. Our paradigm, which separately manipulated the benefit (cue) and the cost indicates that

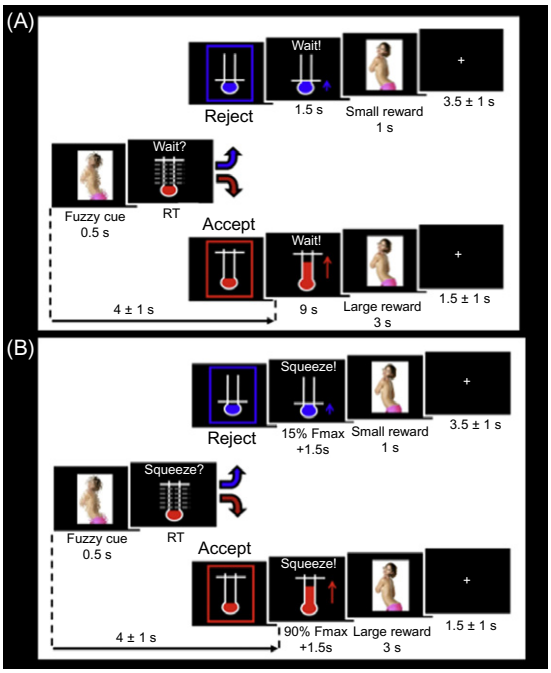

FIGURE 5

Delay discounting (A) and effort discounting (B) paradigms using primary rewards. On each trial, a fuzzy erotic picture briefly appeared on a screen and was followed by the instruction "Wait?" or "Squeeze?," together with a thermometer indicating one of six possible levels of the proposed delay period to wait or effort to invest (ranging from 1.5 to 9 s for the delay and from 15% to 90% of subjects' maximal strength for the effort). Depending on the incentive cue and the proposed level of cost, subjects chose between the costly option and a default option having a minimal cost (1.5 s of waiting or 15% of maximal strength to exert). Then, they either waited passively during the delay period or produced the effort, before seeing the erotic picture clearly for a short time period (small reward) if they rejected the costly option, or a longer period of time (large reward) if they accepted it. The outcome and the intertrial interval lasted for a total of 4.5 s plus a jitter of ±1 s in both options, avoiding that subjects adopted the strategy of choosing more the default option to see more pictures.

*Figure taken from Prevost et al. (2010) ***with permission.*

during the effort condition, ventral striatal and vmPFC responses correlate neither with the subjective value of the effortful reward nor with the level of proposed effort. This result demonstrates that the ventral striatal value signal is not discounted by effort, and two recent rodent studies have come to a similar conclusion (Gan et al., 2010; Walton et al., 2009). In particular, ventral striatal phasic dopamine release has been reported to reflect the magnitude of the benefit, but not the expected effort (Gan et al., 2010). Consistent with this finding, ventral striatal activity positively correlated

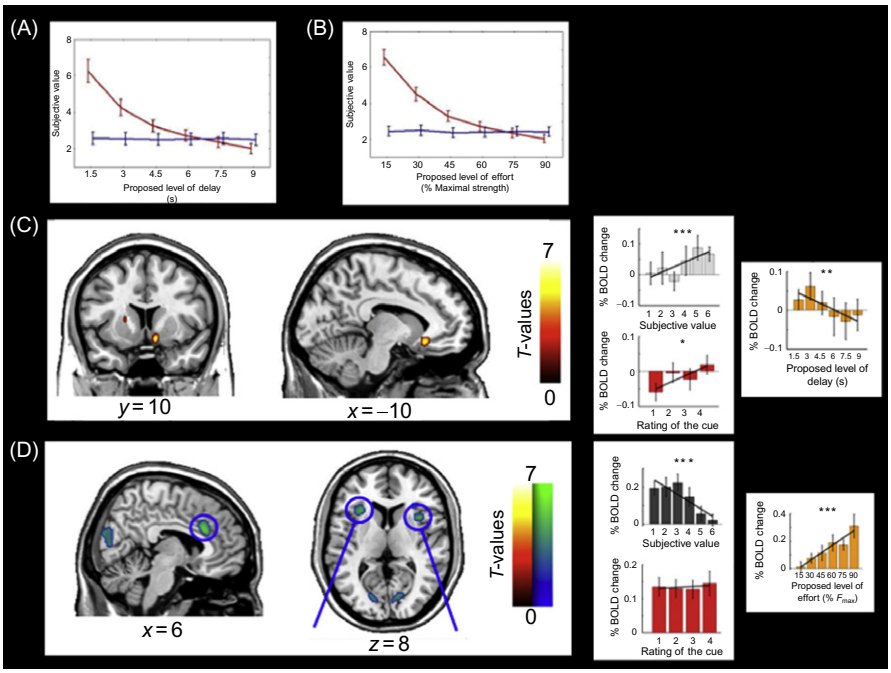

FIGURE 6

Separate valuation subsystems for delay and effort decision costs. Top: Subjective value of rewards associated with the two available options according to the proposed level of delay (A) and effort (B). The red/blue lines represent the subjective value of the reward associated with the costly/default option. Middle (C) Results from the parametric regression analysis showing areas in which activity is positively correlated with the subjective value of delayed rewards. Activity in the ventral striatum and ventromedial prefrontal cortex increases as the subjective value of delayed rewards increases. (C) Right: Plots of the β values representing the slope of the linear regression between neural activity and the subjective value of the delayed reward (light gray), the rating of the cue (red), and the proposed level of delay (orange) in each ROI. (D) Results from the parametric regression analysis showing areas in which activity is negatively correlated with the subjective value of the reward associated with the costly effort. Activity in the anterior cingulate cortex and bilateral insula decreases as the subjective value of effortful rewards increases. (D) Right: Plots of the β values representing the slope of the linear regression between neural activity and the subjective value of the effortful reward (dark gray), the rating of the cue (red), and the proposed level of effort (orange) in each ROI.

Figure adapted from Prevost et al. (2010) with permission.

with the rating of the cue (benefit) in both the delay and effort conditions but was not modulated by the proposed level of effort in our experiment. Thus, our current results help to pinpoint the specific roles of brain regions specifically involved during the valuation stage of decisions related to delay and effort costs.

Our delay-discounting findings suggest that subjective valuation signals of erotic rewards really experienced inside the scanner are computed in similar limbic fronto-striatal networks than nonexperienced secondary (monetary) rewards, delayed from minutes to month/years (Kable and Glimcher, 2007). Therefore, the neural response to both primary and secondary reinforcers follows similar delay-discounting functions, suggesting that valuation of delayed rewards may obey common basic principles of neuronal computation, regardless of the reward nature and the delay duration incurred before reward delivery. In contrast, our effort-discounting results demonstrate a critical role of the ACC–anterior insula network for evaluating whether or not it is worth producing a given effort for the reward at stake. This implies that the ACC is not merely involved whenever it is necessary to evaluate two competing options but instead specifically when evaluating the benefits of exerting more effort for a higher reward as compared to a less rewarding option that requires less energy expenditure.

In summary, our data shed new light on value-based decision-making signals in the human brain by revealing that distinct valuation subsystems are engaged for different types of costs and code in opposite fashion-delayed rewards and future energetic expenses. From an evolutionary perspective, separate valuation systems may have evolved through the need of responding to distinct types of costs in different environments. For example, some primate species are willing to tolerate delay costs but are less inclined to exert more effort and to travel farther to obtain greater reward, while the opposite is true for other species (Stevens et al., 2005). Finally, our demonstration that separate neural systems track the subjective value of rewards associated with different types of costs may prove useful for understanding impulsive (delay aversion) and apathetic (effort aversion) behavior in a number of neuropsychiatric disorders known to impair the capacity to select between available options based on an evaluation of their potential costs and benefits (Paulus, 2007).

5 A COMMON NEURAL CURRENCY IN THE HUMAN BRAIN?

As noted previously, our behavior is motivated by rewards of different nature among which we frequently need to choose. Because there is no single sense organ transducing rewards of different types, our brain must integrate and compare them to choose the options with the highest subjective value. It has been proposed that the brain may use a "common reward currency" that can be used as a common scale to value diverse behavioral acts and sensory stimuli (Sugrue et al., 2005). The need for this common currency arises from the variety of choices we are facing in our daily life.

Recent behavioral studies in monkeys showed that monkeys differentially value the opportunity to acquire visual information about particular classes of social images. Male rhesus macaques sacrificed fluid for the opportunity to view female perinea and faces of high-status monkeys, but required fluid overpayment to view the faces of low-status monkeys. This work uses a behavioral method to quantify how nonhuman primates are likely to weigh one type of reward against another (Deaner et al., 2005). In humans, looking at other people can also be rewarding, and the opportunity to view pictures of the opposite sex is discounted by the duration

of the delay to view the pictures (Hayden and Platt, 2007). Attributing value to available options is impaired by orbitofrontal cortex lesion and recent electrophysiological results indicate that some neurons in the orbitofrontal cortex encode the values of offered and chosen goods (Padoa-Schioppa and Assad, 2006). Moreover, when a monkey is offered one raisin versus one piece of apple, neurons in the orbitofrontal cortex encode the value of the two goods independently of visuospatial factors and motor responses (contrary to other brain areas in which value modulates activity related to sensory or motor processes). These results make an essential distinction between choosing between goods and choosing between actions. In addition, a classical and general question is how the neuronal representation of value depends upon behavioral context. Although some authors have proposed that the encoded value in the orbitofrontal cortex is relative (Tremblay and Schultz, 1999), recent work suggests that neuronal responses in the orbitofrontal cortex are typically invariant for changes of menu, that is, orbitofrontal neuronal response to one particular good usually does not depend on which other goods are available at the same time (Padoa-Schioppa and Assad, 2008). These authors proposed that orbitofrontal neuronal activity encodes economic value rather than relative preference.

Because of the properties mentioned above, the orbitofrontal cortex is likely to be an important brain structure involved in the comparison between different types of goods. However, all the electrophysiological and brain imaging studies published so far compared choices between goods of identical nature (e.g., only food items). Yet, based on the "common currency" concept, there should be a common brain network coding for different types of goods. Many fMRI studies are consistent with this idea, since common brain structures are involved in reward processing, regardless of reward nature. For example, increased midbrain, ventral striatum, and orbitofrontal activities have been observed with different types of rewards, such as monetary gains (Abler et al., 2006; Dreher et al., 2006; O'Doherty, 2004), pleasant taste (McClure et al., 2003; O'Doherty, 2003), visual erotic stimuli (Karama et al., 2002; Redoute et al., 2000), beautiful faces (Bray and O'Doherty, 2007; Winston et al., 2007), drugs such as cocaine (Kufahl et al., 2008; Risinger et al., 2005) as well as pain relief (Seymour et al., 2004, 2005, 2007). However, all these neuroimaging studies only investigated one reinforcer at a time and did not compare any two of these reinforcers directly. This was precisely the goal of a recent fMRI study we performed to compare the common and distinct brain networks involved in processing primary and secondary rewards (Sescousse and Dreher, 2008; Sescousse et al., 2010).

6 ONE OR SEVERAL REWARD SYSTEMS? SPECIFIC ORBITOFRONTAL REGIONS CODE EXPERIENCED VALUE FOR PRIMARY AND SECONDARY REWARDS

Humans are motivated by a wide range of vegetative rewards (such as food and sex) and nonvegetative rewards (such as money, power, fame, etc.). However, it is unclear whether different types of reinforcers recruit distinct or common neural circuits

(Fig. 7). For example, in a recent study, we compared brain activations to monetary gains and erotic pictures in an incentive delay task (Sescousse et al., 2010). Despite their critical sociobiological importance, visual sexual stimuli have never been studied as reinforcers, but rather as arousing stimuli in passive viewing paradigms

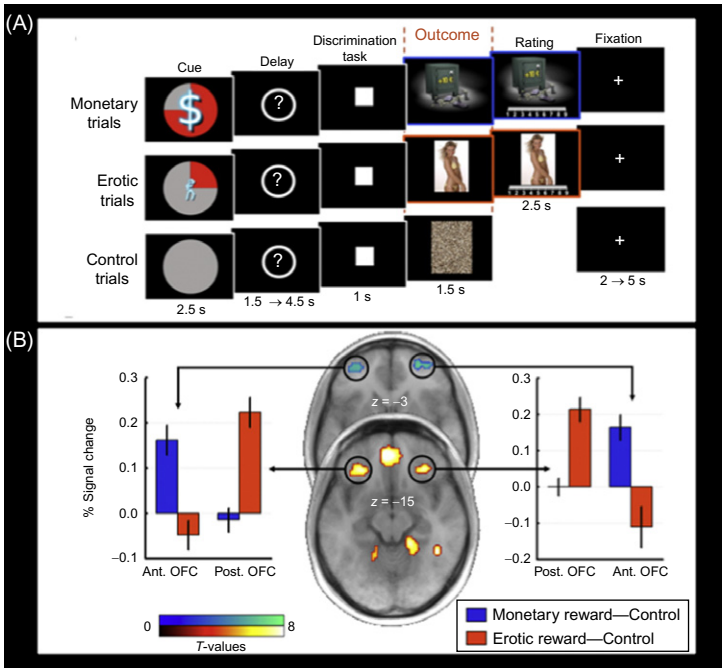

FIGURE 7

Antero-posterior dissociation within the orbitofrontal cortex according to reward nature. (A) Task design. Subjects first saw a cue informing them about the type, probability, and intensity of an upcoming reward. Three cases are represented here: a 75% chance of receiving a high amount of money (top), a 25% chance of seeing a low erotic content picture (middle), and a sure chance of getting nothing (control trials; bottom). After a short delay and a target discrimination task, subjects saw the outcome, which was contingent on both the announced probability and their performance on the discrimination task. Reward outcomes consisted either in a monetary amount displayed on a safe (top) or an erotic picture (middle) and were followed by the rating of their subjective value on a continuous scale. Nonrewarded and control trials displayed a scrambled picture at outcome (bottom). (B) The anterior orbitofrontal cortex codes secondary reward (money), while the posterior and medial orbitofrontal cortex code primary reward (erotic stimuli). Brain regions specifically activated by monetary rewards outcomes are shown in blue-green, and those specifically activated by erotic rewards are shown in red-yellow. Mean percent signal change shows an interaction between reward type and orbitofrontal cortex region in both the left and right sides of the brain. Error bars indicate standard error to the mean.

Figure taken from Sescousse et al. (2010) with permission.

focusing on sexual function. They can be considered as "primary rewards," in the sense that they have an innate value and satisfy biological needs. Conversely, money is defined as a "secondary reward," because its value is more abstract and needs to be learned by association with primary rewards.

We hypothesized that monetary and erotic outcomes would activate both shared and distinct cerebral networks. Based on recent fMRI studies, we hypothesized that core components of the reward system, such as the midbrain, ventral striatum, and ACC would form the core of the shared network ("common currency" network). We also hypothesized a functional dissociation within the orbitofrontal cortex based on a meta-analysis of neuroimaging studies involving different types of rewards. This meta-analysis proposed a postero-anterior dissociation in the orbitofrontal cortex, with more complex or abstract reinforcers being represented more anteriorly than less complex reinforcers (Kringelbach, 2005). That is, we expected erotic rewards to activate more robustly the posterior part of the orbitofrontal cortex, while the more anterior part of this brain region would be more engaged by secondary rewards. In addition, a crucial question was to know whether the neural correlates of PE and expected value could be identified for visual erotic stimuli, which cannot be ascribed an objective value (unlike the amount of monetary reward).

To test our hypotheses, we designed an fMRI experiment comparing brain responses to monetary and visually erotic rewards. Young heterosexual males performed a new event-related fMRI paradigm varying reward nature (money vs. erotic stimuli), reward probability and reward intensity. The structure of each trial was as follows. During anticipation, a cue carried information about the type (monetary or erotic), the probability (0.25, 0.50, or 0.75), and the intensity (high or low) of the upcoming reward. Subjects then had to perform a simple discrimination task by pressing a specified response button for a visual target. At the time of the outcome, they were presented either with "scrambled" pictures (no reward), erotic images, or a picture of a safe indicating an amount of money. At that time, they also had to rate the reward value (of money or erotic stimuli) on a continuous scale.

At the time of outcome, robust BOLD signal was observed for both rewards in a brain circuit including the striatum, the ACC, the midbrain, and the anterior insula. These regions showed a parametric response with the hedonic value, consistent with the idea of a "common neural currency." Moreover, as expected, an antero-posterior dissociation was observed in the lateral orbitofrontal cortex at the time of reward outcome, monetary gains being specifically represented in the anterior part of the orbitofrontal cortex, while erotic pictures eliciting activation in its posterior part. This result is important because it identifies a new functional division within the orbitofrontal cortex, with more anterior regions supporting secondary rewars and evolutionarily more ancient orbitofrontal region representing experienced value of primary reward.

Another key finding of this study is that PE was computed in similar brain regions for monetary and for erotic rewards. PE was defined as the absolute difference between the outcome value and the prediction, where the outcome value was measured by the hedonic ratings and the prediction by the product of expected reward intensity by probability. Brain activity in the ventral striatum, anterior insula, and ACC was

shown to positively correlate with PE, suggesting that PE signals might be essentially computed in the brain regions commonly activated by both rewards. These results extend the concept of PE to erotic rewards and expand our understanding of reward functions by showing that a common brain network is activated by nonvegetative and vegetative rewards, and that distinct orbitofrontal regions respond differentially to various kinds of rewards.

These results are interesting when considering a recent fMRI study suggesting that there may be a single valuation system that discounts future rewards (Kable and Glimcher, 2007). Another fMRI study supports the idea of a "common neural currency" for two types of rewards (Izuma et al., 2008). This study showed that the acquisition of one's good reputation robustly activated reward-related brain areas, such as the striatum, and these areas overlapped with those activated by monetary rewards. In summary, these studies together with a recent meta-analysis of functional neuroimaging studies from our group comparing the neural structures engaged by different primary and secondary rewards suggest that individuals use some of the same circuits to process money and other types of rewards, in the absence of choice between them (Sescousse et al., in press).

7 FROM PERCEPTUAL DECISION MAKING TO VALUE-BASED DECISION MAKING

Perceptual decisions are made when sensory evidence accumulated over time reaches a decision threshold. Because decisions are also guided by prior information, one important factor that shapes how a decision is adaptively tuned to its context is the predictability of forthcoming events. Mathematical models of decision making predict two possible mechanisms supporting this regulation: an adjustment of the distance to the decision threshold, which leads to a change in the amount of accumulated evidence required to make a decision or a gain control of the sensory evidence, leading to a change in the slope of the sensory evidence accumulation. We recently showed that predictability of the forthcoming event reduces the distance to the threshold of the decision (Domenech and Dreher, 2010). Using model-driven fMRI, we found that the BOLD response in the ACC correlates with the distance to the decision threshold but not with the slope of sensory evidence accumulation, suggesting that this brain region adjusts the distance to the threshold to the current amount of predictive information. Moreover, the dorsolateral prefrontal and intraparietal cortices accumulated sensory evidence over time.

One important remaining issue is to integrate the approach of sequential sampling model of perceptual decision making and value-based decision making in a general framework. Our hypothesis is that models of perceptual decision, such as sequential sampling models, can be extended to value-based decision making by proposing that the distance between options modulates the slope of the sensory evidence accumulation. When the outcomes of options are uncertain, we must also consider the degree of uncertainty present. According to sequential sampling models, choices are the

result of a dynamic process during which the decision maker compares options against each other to update a preference state. In contrast, economic theories (such as prospect theory) explaining why people's decisions under risk deviate from standard economic view of expected utility maximization may be limited because they do not explain the probabilistic nature of preferential choice, that is, why an individual makes different choices in nearly identical situations, nor why these "irrational" choices are more frequent when uncertainty increases. We have recently designed a new study investigating how different value-related signals are computed in the brain when making value-based choices, focusing on the representation of the subjective distance between options, the subjective value of the chosen option, and choice uncertainty (Domenech and Dreher, 2008). This fMRI paradigm investigates choice behavior between options leading to different types of probabilistic primary rewards. Briefly, young heterosexual males, drink deprived for 12 h, were scanned in a new fMRI paradigm while choosing between two gambles, one rewarded by a very small amount of fruit juice (0.5 ml) and the other by visual erotic stimuli (pictures of naked women). Participants experienced both types of primary rewards directly inside the scanner. For each trial, two pie charts indicated the reward probabilities, varying independently (e.g., $P = 0.75$ juice vs. $P = 0.5$ erotic stimulus). One important aspect of the task is that the magnitude of the reward was kept constant. Therefore, choices were made on the basis of preference for a type of reward and on the basis of reward probability.

We first estimated the preference of each participant for fruit juice over an erotic picture and expressed it as an equivalent offer, by fitting, for each participant a logistic model of the probability of choice that included the probability of being rewarded by the fruit juice, the erotic picture and the trial number as explanatory variables. This last variable accounted for a possible drift of the preference during the experiment and was included in the model as a control. The preference was computed as the ratio of the parameter estimates for the picture and drink. Then, the subjective distance between options for each offer was computed as the difference between the subjective value of the juice option and the subjective value of the erotic picture option.

Behavioral results indicated that participants had heterogeneous preferences, some preferring juice over pictures, others pictures over juice. Response times increased linearly with choice uncertainty, indicating that the decision process slows down as the subjective distance between options decreases and as it becomes harder to discriminate which option is the best. Conversely, response times decreased as the subjective value of the chosen option increased, reflecting higher motivation for the favored choice. Moreover, the proportion of choice of a given option varied as a sigmoidal function of the distance between the subjective values of each option, showing that probability of choice is effectively modulated by the difference between subjective values of the available options.

The brain imaging results revealed that, with increasing difference between subjective values, activity increased in the medial anterior and lateral parts of the orbitofrontal cortex and the midbrain, reflecting computation of the distance between

options in a "common currency" space. The same orbitofrontal regions coding the subjective distance between options at the time of decision also coded the subjective value of the chosen option.

Moreover, brain regions coding choice uncertainty involved the ACC, the bilateral anterior insula, and the inferior frontal gyri. This activity is likely to reflect the slowing down of the decision process observed behaviorally. Importantly, BOLD activity in the orbitofrontal cortex did not correlate with choice uncertainty, even when lowering the statistical threshold. Overall, these results indicate a functional dissociation between two brain networks: the orbitofrontal cortex, which codes the subjective values related to the goal of the decision and the ACC/anterior insula network, which codes the uncertainty on these values. These results indicate that the same orbitofrontal cortex region codes different value-related signals and emphasizes a brain network composed of the ACC and the anterior insula that computes choice uncertainty.

To conclude, the studies reviewed above indicate that the human orbitofrontal cortex is not only involved in processing a number of value signals, such as the subjective values of stimuli, but also contributes to processing signals related to the decision making process itself, such as the distance between the subjective value of different options, thereby coding signals informing about what action to take next.

8 VARIATION IN DOPAMINE GENES INFLUENCE REWARD PROCESSING

Both reward processing and decision making engage brain structures that lie on the ascending dopaminergic pathways. An important axis of current research is to study the brain influence of genes that affect dopaminergic transmission in order to clarify the biological mechanisms underlying interindividual differences and vulnerability to pathology related to the dysfunction of the dopaminergic system (Caldu and Dreher, 2007). Although there are clear individual genetic differences regarding susceptibility to and manifestation of these neuropsychopathologies, the influence of genetic predispositions and variations on activation of the human reward system remains poorly understood.

Recent neuroimaging and behavioral studies have focused on the genetic variations of dopamine receptors, especially DRD2 and DRD4, and a number of genes coding for enzymes and transporters involved in the dopaminergic transmission, such as the catechol-*O*-methyltransferase (*COMT*) and the dopamine transporter (*DAT*). For example, polymorphisms in dopamine receptor (DRD4) and monoamine oxidase A (*MAOA*) genes showed significant associations with efficiency of handling conflict as measured by reaction time differences in an attention task and modulate ACC activation (Fan et al., 2003). Moreover, the role of the DRD2

polymorphism in monitoring negative action outcomes and feedback-based learning was tested during a probabilistic learning task (Klein et al., 2007). A1-allele carriers, with reduced dopamine D2 receptor densities, showed lower posterior medial frontal cortex activity, involved in feedback monitoring, and learned to avoid actions with negative consequences less efficiently. The authors suggested that dopamine D2 receptor reduction seems to decrease sensitivity to negative action consequences, which may explain an increased risk of developing addictive behaviors in A1-allele carriers. Recent behavioral and computational modeling works also suggest independent gene effects (DARPP-32, DRD2, COMT) on reinforcement learning parameters that contribute to reward and avoidance learning in humans. These findings support a neurocomputational dissociation between striatal and prefrontal dopaminergic mechanisms in reinforcement learning (Frank et al., 2007), proposing that prefrontal dopamine is involved in regulating exploration, while striatal dopamine is involved in learning. In line with this view, Humphries et al. (2012) showed that tonic dopamine in the basal ganglia can also participate in the regulation of the exploration–exploitation trade-off.

Two important proteins contribute to terminating the action of intrasynaptic dopamine in the brain: COMT, which catabolizes released dopamine, and the DAT, which plays a crucial role in determining the duration and amplitude of dopamine action by rapidly recapturing extracellular dopamine into presynaptic terminals after release. In humans, the *COMT* gene contains a common and evolutionarily recent functional polymorphism that codes for the substitution of valine (val) by methionine (met) at codon 158, referred to as $Val^{158}Met$ polymorphism. The COMT enzyme is involved in the metabolic degradation of catecholamines, converting dopamine into 3-methoxytyramine and norepinephrine into normetanephrine. Because the COMT protein containing methionine is relatively thermolabile, its activity is lower at body temperatures than the COMT valine protein, which is fully active at body temperature. Hence, individuals with two copies of the met allele (met/met) have 25–75% reduction in COMT enzyme activity, and therefore presumptively more baseline synaptic dopamine, compared to individuals with two copies of the val allele (val/val) (Chen et al., 2004; Lachman et al., 1996).

The *DAT*1 gene (SLC6A3) includes 15 exons, with a variable number of tandem repeat (VNTR) polymorphisms in the 15th exon, a region encoding the transcript's 3′ UTR (Vandenbergh et al., 1992). The 40-bp VNTR element is repeated between 3 and 13 times but in most of the population occurs with greatest frequency in the 9- and 10-repeat forms. The expression of the *DAT*1 9-repeat allele is lower than the 10-repeat allele (Heinz et al., 2000; Mill et al., 2002; VanNess et al., 2005), although one study reported the opposite allelic associations (Van Dyck et al., 2005). Thus, the *DAT*1 10-repeat allele, associated with increased expression of the gene, presumably leads to relatively decreased extrasynaptic striatal dopamine levels. This is consistent with a human SPECT study reporting increased striatal DAT availability in 9-repeat carriers relative to 10-repeat carriers (Jacobsen et al., 2000), although another study failed to support this (Heinz et al., 2000). Mice lacking the *DAT*1 gene

show extensive adaptative changes in the dopaminergic system, the DAT controlling both the duration of extracellular dopamine signals and regulating presynaptic dopamine homeostasis (Jones et al., 1998).

Importantly, animal studies indicate differential functional localization of the COMT and DAT proteins. The COMT enzyme plays a particular role in modulating dopamine in the PFC, where *DAT*1 expression is sparse (Karoum et al., 1994; Matsumoto et al., 2003b). *COMT* is expressed more abundantly in cortical neurons than in the striatum (Matsumoto et al., 2003a), but it is unclear to what extent *COMT* modulates catecholamine function outside the cortex. Recent studies in COMT knockout mice suggest that COMT has little if any role in striatal dopamine levels (Yavich et al., 2007). In contrast, animal research and human postmortem studies indicate that the *DAT*1 is expressed abundantly in midbrain, striatum, and hippocampus but sparsely in the PFC (Schott et al., 2006; Sesack et al., 1998).

In parallel with the fundamental fMRI results concerning PE mentioned before, fMRI studies in healthy young subjects have documented that distinct reward anticipation- and outcome-processing phases are associated with differential patterns of specific midbrain dopaminergic postsynaptic targets (Dreher et al., 2006; Knutson et al., 2003; O'Doherty et al., 2002). Specifically, anticipation of reward robustly activates foci in the ventral striatum (Knutson et al., 2003; O'Doherty et al., 2002), particularly during anticipation of rewards with maximal uncertainty (i.e., reward probability = 0.5) (Dreher et al., 2006), while rewarded outcomes activate the lateral and orbital parts of the PFC (Dreher et al., 2006; Knutson et al., 2003). Despite the direct involvement of the COMT and DAT proteins in dopamine transmission, the influences of *COMT* and *DAT*1 functional polymorphisms on distinct components of the reward system have not been as systematically explored as have been the domains of working and episodic memory (Bertolino et al., 2006; Caldu et al., 2007; Schott et al., 2006).

Although there are clear individual genetic differences regarding susceptibility to and manifestation of these neuropsychopathologies, the influence of genetic predispositions and variations on activation of the human reward system remains poorly understood. Investigating the effects of interindividual differences in dopamine signaling on the response of the reward system is thus an important research question because these differences may contribute to heritable personality traits in the general population and to neuropsychiatric conditions involving abnormalities in catecholamine neurotransmission, such as substance abuse, mood disorders, obsessive compulsive disorder, attention deficit hyperactivity disorder, and schizophrenia. Using event-related fMRI and a recently developed reward paradigm, we directly investigated the relationship between *COMT* and *DAT*1 functional polymorphisms and the response of the reward system during anticipation of uncertain rewards and, at the time of reward delivery, bridging the gap between basic molecular genetics, fundamental electrophysiological findings, and functional neuroimaging in humans (Dreher et al., 2009). The results revealed a main effect of *COMT* genotype in the ventral striatum and lateral PFC during reward anticipation, and in the orbitofrontal cortex at the time of reward delivery, met/met individuals exhibiting the highest

activation (Fig. 8). The main effect of COMT genotype both in the ventral striatum and lateral PFC is consistent with the hypothesis that dopamine regulates exploration both through the PFC and basal ganglia (Frank et al., 2007; Humphries et al., 2012).

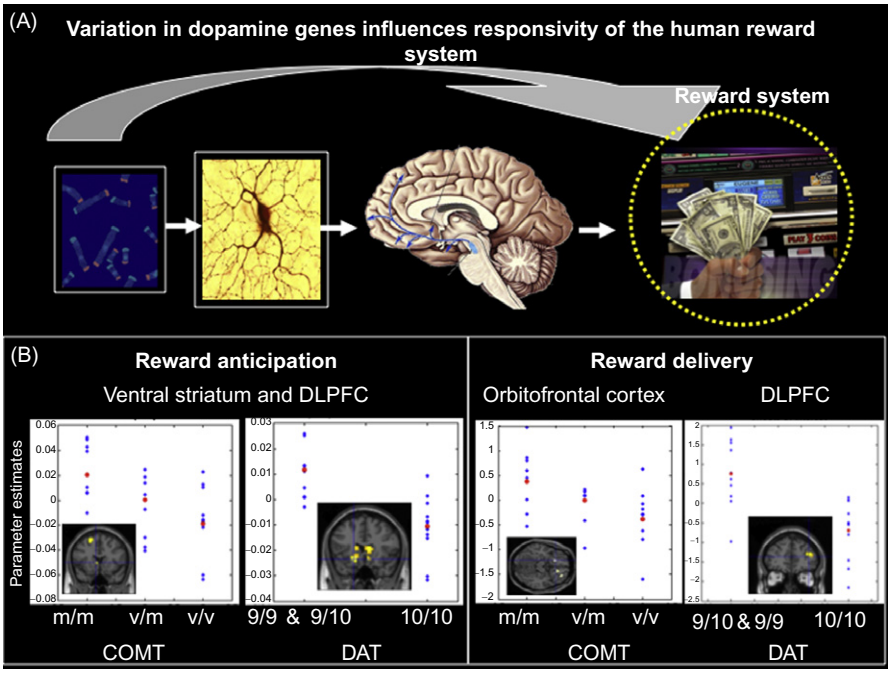

FIGURE 8

(A) Relationships between the effects of genetic variations and reward processing. Influence of the polymorphisms of the catecholamine-*O*-methyltransferase (COMT) (valine/valine; valine/methionine; methionine/methionine) and the Dopamine Transporter (9/9 & 9/10; 10/10) on the reward system. (B) Left: Main effect of *COMT* and *DAT* genotypes during anticipation of reward with maximal uncertainty. Negative relationship was observed between *COMT* val allele dosage (0_met/met, 1_val/met, or 2_val/val) and BOLD response in the ventral striatum, left superior PFC, and dorsolateral PFC during anticipation of reward with maximal uncertainty. More robust BOLD response was observed in 9-repeat carriers (including *DAT*1 9-repeat and 9/10) compared to 10-repeat individuals during reward anticipation in the bilateral ventral striatum. Right: Main effect of *COMT* and *DAT* genotypes at the time of reward delivery. Negative relationship between *COMT* val allele dosage and orbitofrontal cortex activation at the time of reward delivery. Higher lateral prefrontal BOLD signal was observed in *DAT*1 9-repeat allele dosage compared to 10-repeat carriers at the time of reward delivery.

Figure adapted from Dreher et al. (2009) with permission.

The main effect of *DAT*1 genotype was seen in robust BOLD response differences in the caudate nucleus and ventral striatum during reward anticipation, and in the lateral PFC and midbrain at the time of reward delivery, with carriers of the *DAT*1 9-repeat allele showing the highest activity. Moreover, an interaction between the *COMT* and *DAT*1 genes was found in the ventral striatum and lateral PFC during reward anticipation and in the lateral prefrontal and orbitofrontal cortices as well as in the midbrain at the time of reward delivery, with carriers of the *DAT*1 9-repeat allele and *COMT* met/met allele exhibiting the highest activation, presumably reflecting functional change consequent to higher synaptic dopamine availability.

One important insight provided by our data is a clear demonstration of interaction between the *DAT*1 and *COMT* genes that control a complex phenotype (activation of the reward system). This interaction likely reflects differences in dopaminergic level due to the combined effect of the *COMT* val/val and *DAT*1 10/10 alleles on elimination of dopamine in the fronto-striatal system. Interestingly, the effects on the BOLD signal of this presumed low dopamine level in val/val and 10-repeat alleles' carriers differ both according to brain regions and task phases.

These results indicate that genetically influenced variations in dopamine transmission modulate the response of brain regions involved in anticipation and reception of rewards and suggest that these responses may contribute to individual differences in reward-seeking behavior and in predisposition to neuropsychiatric disorders.

A recent study used a guessing task to investigate how individual variation in *COMT* and *DAT*1 genes influences reward processing (Yacubian et al., 2007). In accordance with our results, this study reported that, during reward anticipation, the lateral PFC and the ventral striatum activities were *COMT* genotype-dependent: subjects homozygous for the met allele showed higher responses in these brain regions compared with volunteers homozygous for the val allele. This effect was observed when averaging all probabilities and magnitudes against baseline, but no main effect of *COMT* genotype was observed on ventral striatal sensitivity to reward uncertainty. Moreover, no main effect of *DAT*1 genotype was reported on striatal activity during reward anticipation, despite the well-established abundancy of DAT in the striatum. A gene–gene interaction between *COMT* and *DAT*1 was observed in the ventral striatum when sorting genotypes from met/met *DAT*1 10-repeat allele to val/val 9-repeat allele, interpreted as consistent with the notion that basal dopaminergic tone, regulated by *COMT*, interacts with phasic dopamine release, regulated by the *DAT*. It is difficult to directly compare our findings to these results because *COMT* and *DAT*1 genotypes may both directly influence distinct components of the human reward system (COMT modulating the dorsolateral PFC and DAT the striatum) and differentially affect their neurofunctional balance in a task-dependent manner. Finally, since this previous study did not report effects of genotype on fMRI results at the time of reward delivery, it remains unclear whether distinct phases of this guessing task induce differential brain activity dependent upon *COMT* and *DAT*1 polymorphisms.

It should be noted that our fMRI results on COMT/DAT genotypes cannot establish the neurophysiological mechanisms underlying the relationship between dopamine release and BOLD signal increase (Knutson and Gibbs, 2007). However, our

study directly links genotype-dependent synaptic dopamine availability with BOLD signal change in humans and suggests that higher BOLD signal at prefronto-striatal sites is associated with greater dopamine synaptic availability (i.e., lower dopamine elimination), in agreement with recent studies observing that (a) in young adults there is a tight coupling between increased midbrain dopamine synthesis and reward-related increased BOLD signal in the PFC both during reward anticipation and at the time of reward delivery (Dreher et al., 2008) and (b) in animals injection of dopamine-releasing agents increases BOLD signal in mesolimbic regions with a time course that parallels the changes observed by microdialysis measurements of striatal dopamine release (Chen et al., 1997).

9 CONCLUSIONS

In this chapter, I have described neuroimaging evidence of computational factors affecting valuation and decision-making signals. The integrity of the neural structures computing these value signals are crucial for efficient decision making and for processing of reward information. A better knowledge of the neural basis of value signals, PE, and uncertainty signals is likely to advance our understanding of the impact that different types of neuropathologies have on reward and decision making. Clinical areas of research in which the current knowledge on value-based decision making can be applied concern a variety of neuropathologies, such as schizophrenia, Parkinson's disease, pathological gambling, or drug addiction.

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