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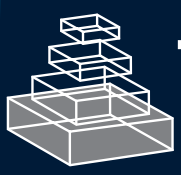
RESEARCH TOPICS

BEHAVIORAL AND NEUROSCIENTIFIC ANALYSIS OF ECONOMIC DECISION MAKING IN ANIMALS

Topic Editors
Tobias Kalenscher and Marijn Van Wingerden



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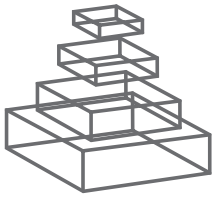

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BEHAVIORAL AND NEUROSCIENTIFIC ANALYSIS OF ECONOMIC DECISION MAKING IN ANIMALS

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The experimental analysis of animal behavior has a rich tradition in psychology, behavioral ecology and many other scientific branches dedicated to the study of decision making. However, it has never enjoyed a similar popularity in economics. This has recently changed with the dawn of neuroeconomics – a discipline combining the analytic and experimental tools of psychology and economics with the technologies available in neuroscience to unravel the neurobiological mechanisms underlying economic behavior.

Since many of the sophisticated neuroscientific techniques can only be used on animals, neuroeconomists have come up with a large and ever-growing repertoire of animal models to probe economic decision making. Besides the value of using animals as model systems to emulate human economic behavior, the discipline of animal economic decision making exists in its very own right: an abundance of animal species at various evolutionary stages show behavior that complies with many of the predictions of economic theory, whilst, at the same time demonstrating violations of optimal choice models that are reminiscent of similar anomalies found in human behavior. Hence, the analysis of animal choice does not only offer insights into the evolutionary origins of economic decision making, it also testifies that the analysis of animal behavior is a convenient, economical and sound way to test competing economic decision models in optimally controlled experimental environments, to probe their neural implementation and to yield common denominators in choice behavior.

In short, economic theory provides more than just an alternative language to describe animal psychology: its combination with biology, psychology and neuroscience gives way to synergy effects that open up new venues for studying economic choice. In this special issue, we would like to gather the latest results from this cross-disciplinary topic, address the overlap and discrepancies in (the neurobiology of) economic decision making found between species and identify the challenges that lie ahead in translating results from species to species, and ultimately to humans.

The exclusive focus on non-human animals makes this Research Topic unique and distinct from previous special issues which covered a broader range of matters and subjects in the neurobiological analysis of decision making.

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EDITORIAL
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Animal decisions – a look across the fence

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In this Research Topic, we have gathered some of the latest experimental results obtained in the exciting arena of studying decision-making in animals. With the dawn of the neuroeconomic method (Glimcher and Rustichini, 2004), a parallel track, or perhaps *many* parallel tracks have emerged where decision-making processes in non-human animals are being investigated. A wealth of experimental data indicates that the idiosyncrasies of human decision-making are largely mirrored in animal choice behavior, thereby both firmly establishing animal models as relevant to the study of human decision-making, and as an avenue into comparative studies of the evolution of decision-making processes. In this issue, up-to-date reviews and brand new research are mixed, featuring studies into decision-making with a cast of species spanning the animal kingdom.

Kalenscher and van Wingerden (2011) open with a review of the two points mentioned above: the similarities between humans and other animals in (deviations from) optimal choice behavior as predicted by economic theory, and the evolutionary roots of human decision-making. Highlighting differences and commonalities between species in choice behavior could help to understand the evolutionary roots of human decision-making, and perhaps help to explain why humans sometimes tend to deviate from strictly optimal choice behavior in contemporary decision-making contexts.

Next, Shizgal (2012) illustrates this comparative approach by taking a single paradigm, intracranial self-stimulation as the pursuit of a good with scarce means (operationalizing time as a handling cost). Shizgal illustrates how the behavior of the animals in this setting can be described by a component functional model, with proposed neural implementation, that incorporates the modulation of the allocation of time by reward magnitude and opportunity costs.

One has to be careful in the translation of experimental paradigms between humans and non-human animals, however, as illustrated by the report of Calvert et al. (2011). Using pigeons, these authors report that explicitly signaling the duration of common and unique delays in an intertemporal choice paradigm was sufficient to reproduce the finding in human subjects that adding a common delay to an intertemporal choice reduced the degree of discounting of the larger, later reward, whereas refraining from explicit signaling actually produced opposite results. The set of results from the explicitly signaled condition are in line with hyperbolic models of delay discounting and provide strong evidence for evolutionary conserved decision-making processes, but the other results strikingly highlight the pitfalls of assuming that a certain animal paradigm matches experimental conditions in human studies.

It has been widely recognized that most decisions are made in a social context, and that these contexts do influence decision-making. The questions remains whether this influence is restricted to humans or primates, or whether this is a more general theme in animal decision-making. Social foraging theory predicts that an animal's foraging choices are not only influenced by the balance in the rate of food intake versus the effort invested, but also by the presence of conspecifics. In two related papers, Ogura and Matsushima (2011) and Amita and Matsushima (2011) report that social manipulations in chicks did influence reward-related motivation, but not choice allocation, suggesting that at least chicks "keep their cool" in a competitive social context.

While a social context provides an example of an uncertain environment, uncertainty about future (foraging) outcomes has been traditionally operationalized as risk (uncertainty with known probabilities) and ambiguity (uncertainty about probabilities). Burke and Tobler (2011) review existing data on the neural coding of risk and ambiguity, suggesting largely independent coding of these two aspects of uncertainty that influence human and animal decision-making. Adding new experimental data, Hayden et al. (2010) contributed their latest findings on decisions under risk and ambiguity in monkeys. They show that macaques, that are usually risk-seeking display aversion to ambiguity – much like humans in a closely matched experiment with volunteers. The same authors also report the results from a single unit recording study in monkey posterior cingulate cortex (CGp, Heilbronner et al., 2011). Their results challenge the notion that this area tracks subjective value with single unit and population firing rates, as reported earlier. They show that CGp firing rates do not necessarily track the subjective value of options, as inferred from choice data, but rather are best explained by the deviation of the chosen option from a non-risky, non-delayed "standard" option across decision contexts. This deviation, which they dub "decision salience," could be an attentional signal important for modulation of learning from outcomes. It remains to be seen whether such a neural signal exist in other species.

One of the obvious advantages to the study of non-human animals is the wider range of techniques available. Causal contributions of brain regions to decision-making can be carefully isolated and pharmacological manipulations in animals complement genetic studies involving humans suggesting involvement of neurotransmitter systems. In the clinic, one the most widely used assays for testing decision-making capacities in humans is the well-known Iowa Gambling Task. Turning to rats, de Visser et al. (2011c) reviewed four rodent gambling task models (RGTs) attempting

to reproduce the canonical deficits on the Iowa Gambling Task observed by patients. The authors sketch the relative strengths and weaknesses of the four selected empirical models and discuss the translational potential of the rodent versions. In addition, de Visser and a different group of co-workers report novel experimental findings with their RGT model of choice, investigating the role of the rat medial prefrontal cortex (mPFC, de Visser et al., 2011b). They show that pharmacological mPFC inactivation seems to affect the exploitation phase of the RGT, when animals usually maintain responding on the long-term advantageous option in the face of infrequent negative outcomes, but not the exploratory phase thought to rely on a different brain regions (de Visser et al., 2011a).

It would be interesting to study simultaneous neuronal recordings from these areas as the rats proceed through the different choice strategies. However, single neuron recordings come with their own set of pitfalls. Two sets of authors discuss these pitfalls in interpreting single neuron spike data in decision-making experiments. Stüttgen et al. (2011) examined the requirements for "neurometric" data in perceptual decision-making tasks. Single neuron and population spike rates are modulated by stimuli, and usually such neurometric response curves are matched to psychometric response curves, tracking detection, choice or any other observable outcome. But identifying the "right" neurometric (rate, regularity, synchrony), as well as excluding interference between the sensation and its observable outcome are problematic. Wallis and Rich (2011) review the challenges in disambiguating decision related parameters like subjective value, saliency and motor preparation with correlational data like single unit spike recordings. To conclude the contributions, Roesch and Bryden (2011) review results from their studies of the rat single unit neural coding of reward magnitude and delay to reward, two parameters that heavily influence animal decision-making. They report that in most regions, delay to reward and reward magnitude seems to be coded by largely separate pools of neurons. In primates, it was recently shown that neural coding of risk and reward magnitude was largely separate (O'Neill and Schultz, 2010). It remains to be seen whether such decision variables, that appear to be largely integrated in compound imaging techniques such as fMRI, can be dissociated on the neural level in humans as well.

Finally, we have asked the authors of these articles to describe what, in their view, is the most important reason to investigate decision-making processes with the aid of animal experiments. Obviously, the range of techniques available for animal research is considerably larger than for human volunteers. However, even after many years of animal foraging and microeconomic research, we can still be surprised by new paradigms that show similarities between human and non-human decision-making where previously discrepancies were assumed. As mentioned by one of the contributors, and indeed also exemplified by the paper by Calvert et al. (2011), the specific context of our decision-making experiments can make all the difference in finding evidence for less or more temporal discounting, for risk-seeking or risk aversive behavior. Many authors agree that we need to think about the evolutionary context in which decision-making mechanisms evolved to appreciate their adaptive roles: comparative research across species, and thus the understanding of animal decision-making (preferably in ecologically plausible test environments) is therefore a necessary step. Other contributors mentioned that the understanding of derailed decision-making in substance abuse or psychiatric illness also relies heavily on animal research: the pharmacological irregularities found in human brains can be modeled in animals to a high degree and much of the knowledge we have of the functional networks underlying decision-making actually stems from invasive animal research. It that sense, trying to understand the animals equals trying to understand ourselves.

Besides similarities, discrepancies – sometimes large, of course remain: As one of the contributors points out, an important distinction between animal decision-making, as studied in the lab, and real-life decisions made by humans can be the uniqueness and scope of our decisions: is it at all possible to model life-changing, one-shot decisions (such as buying a house) in animals?

With this Research Topic, we hope to give an overview of the exciting research that is being carried out on animal decision-making and its relevance for the understanding of human decisions. Our hope is that researchers in the various disciplines devoted to the study of decision-making – be it economist, biologists, psychologist or other, will continue to decide to "look over the fence" every now and then. There's a world of decisions waiting to be studied.

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Why we should use animals to study economic decision making – a perspective

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Despite the rich tradition in psychology and biology, animals as research subjects have never gained a similar acceptance in microeconomics research. With this article, we counter this trend of negligence and try to convey the message that animal models are an indispensible complement to the literature on human economic decision making. This perspective review departs from a description of the similarities in economic and evolutionary theories of human and animal decision making, with particular emphasis on the optimality aspect that both classes of theories have in common. In a second part, we outline that actual, empirically observed decisions often do not conform to the normative ideals of economic and ecological models, and that many of the behavioral violations found in humans can also be found in animals. In a third part, we make a case that the sense or nonsense of the behavioral violations of optimality principles in humans can best be understood from an evolutionary perspective, thus requiring animal research. Finally, we conclude with a critical discussion of the parallels and inherent differences in human and animal research.

Keywords: neuroeconomics, decision making, animals, reward, optimal foraging, behavioral ecology, ethology, rational

> "The difference in mind between man and the higher animals, great as it is, certainly is one of degree and not of kind."
> *The Descent of Man (Charles Darwin, 1871)*

SIMILARITIES BETWEEN NORMATIVE THEORIES OF DECISION MAKING IN ECONOMICS AND BIOLOGY

WHY STUDY ANIMAL DECISION MAKING?

Do animals make economic decisions? Even though the answer is trivial for students of the cognitive sciences, surprise and skepticism is a common response, not only among lay people, when we answer this question with "yes." Animals don't *think*, so how can they make economic decisions, and why would it be interesting to study them? In very general terms, economics is a discipline that aims to predict how human individual decisions affect the supply and demand of (usually limited) resources. So, what are the reasons for studying animal behavior when one is ultimately interested in theories of human economic decision making?

Of course, monkeys and other animals are widely used in neuroeconomics and economically flavored neuroscience research, often for methodological reasons (see for instance Floresco et al., 1997, 2008; Shizgal, 1997; Leon and Shadlen, 1998; Platt and Glimcher, 1999; Cardinal et al., 2001; Yanagihara et al., 2001; Izawa et al., 2003, 2005; Phillips et al., 2003; Barraclough et al., 2004; Dorris and Glimcher, 2004; Sugrue et al., 2004; Kalenscher et al., 2005, 2006a; McCoy and Platt, 2005; Tobler et al., 2005; Padoa-Schioppa and Assad, 2006; Roesch et al., 2006; van den Bos et al., 2006a, b; Yang and Shadlen, 2007; Kalenscher and Pennartz, 2008; Kim et al., 2008; Gan et al., 2009; Louie and Glimcher, 2010). However, as we will argue in this article, technical reasons are not the only grounds for studying animal choice behavior. In order to fully comprehend the origins of human choice behavior, we should investigate the evolutionary roots of our decision making processes by looking at choice mechanisms and their neural substrates in animals. We maintain that, even though there might exist a many-to-one mapping of neural implementations to choice processes, careful comparisons across species can complement human microeconomics research by supplying possible answers to the question *why* we make decisions as we do.

ASSUMPTIONS IN BIOLOGICAL AND ECONOMIC ACCOUNTS OF CHOICE BEHAVIOR

Animal decision making has traditionally been studied assuming that animals optimize their energy intake and reproductive opportunities under evolutionary pressure, and have adapted their choice behavior accordingly. Hence, many ecological theories of decision making have in common with economic models that they focus on optimality of choice behavior, which gives both schools of thinking a normative flavor. Moreover, both schools share crucial concepts, such as equilibrium states in social exchange (Nash, 1950) or evolutionary strategies (Dawkins, 2006). In that normative tradition, until recently, economic theories departed from the assumption that decision makers have (i) stable preferences over time and context, (ii) are motivated by their material self-interest (iii) are rational (in the sense that they make internally and intertemporally consistent decisions that are in accordance with their own stable preferences), and (iv) that decision makers' choices are made with respect to final states and not with respect to changes of states (in the sense that decisions should not be made with respect to gains or losses, but with respect to the final monetary levels[1]; Friedman and Savage, 1948, 1952; Varian, 2006).

[1]For example, a decision maker should be indifferent between these two cases: (a) an individual has \$0 and wins \$100 (final state \$100), or, (b) an individual is first endowed with \$200 but then loses \$100 of this endowment (final state \$100).

Despite crucial differences, there are remarkable similarities in the assumptions and implications made in economic theories and ecological models of animal foraging in the biological literature (cf. Caraco, 1983; Stephens and Krebs, 1986; Kacelnik, 2006) and, to a somewhat lesser extent, in reinforcement learning models in psychology (Thorndike, 1911; Herrnstein, 1961, 1970; Navarick and Fantino, 1974). We like to illustrate the similarities between the disciplines with two examples: decision making under risk and over time.

DECISION MAKING UNDER RISK: EXPECTED UTILITY THEORY AND RISK SENSITIVITY THEORY

One of the dominant theories in economics for decision making under risk, expected utility theory (EU), formally prescribes choice behavior of decision makers that are assumed to behave as if they maximized expected utility. Expected utility is the sum of the probability-weighted utilities of all possible final states of an option, i.e., after the options' prospects are integrated with the current asset level (von Neumann and Morgenstern, 1944). Assuming concave utility functions (Bernoulli, 1954), EU predicts risk aversion, as illustrated in **Figure 1**.

In biology, classic optimal foraging theory assumes that evolution has favored foraging strategies that maximize the rate of energy intake as a proxy of Darwinian fitness (Charnov, 1976; Cowie, 1977). Since a given food source is progressively depleted with the time spent foraging, the marginal energy gain obtained from a given source is decreasing as a function of foraging time. Hence, the rate of gain, and thus ultimately Darwinian fitness associated with a food source is monotonically rising, but, due to its decreasing marginal gain, decelerating over time spent foraging. However, this alone is not yet sufficient to draw a parallel between optimal foraging and EU. In fact, classic optimal foraging theory posited that animals behaved as if they considered only average outcomes in the environment, and hence ignored outcome variability and risk. Consequently, inconsistent with the empirical reality (Kacelnik and Bateson, 1996; Kacelnik, 1997; Bateson and Kacelnik, 1998), classic optimal foraging models predicted risk-neutral attitudes. Risk-sensitive foraging theory has extended the classic framework of non-linear relationships between Darwinian fitness and energy gain to time- and outcome-variable, risky environments (Stephens, 1981, 2008; Stephens and Krebs, 1986; Kacelnik and Bateson, 1996). According to risk-sensitive foraging theory, if an animal chooses between two food patches offering equal average gains, but differing in outcome variance (risk), then a concave, monotonically increasing and decelerating function linking Darwinian fitness to energy gain would predict risk aversion (**Figure 1A**). Note that accounts referring to skewed memory representations of the risky outcomes can equally well account for risk aversion, but to a lesser extent for risk seeking (Reboreda and Kacelnik, 1991; Bateson and Kacelnik, 1996; Kacelnik and Bateson, 1997).

DECISION MAKING OVER TIME: DISCOUNTED UTILITY THEORY, RATE MAXIMIZATION, AND THE MATCHING LAW

Most of our decisions do not yield immediate outcomes, but outcomes that can only be realized at some point in the future. Literally all human and non-human animals tested devalue (discount) future relative to immediate outcomes (Samuelson, 1937; Knapp et al., 1959; McDiarmid and Rilling, 1965; Chung and Herrnstein, 1967; Rachlin and Green, 1972; Ainslie, 1974, 1975; Benzion et al., 1989; Green et al., 1994; Kalenscher et al., 2005, 2006a, b; Kalenscher and Pennartz, 2008). In economics, the dominant framework for decision making over time is discounted utility theory (DU; Samuelson, 1937; Koopmans, 1960; Lancaster, 1963; Fishburn and Rubinstein, 1982; Prelec and Loewenstein, 1991; Frederick et al., 2002; Kalenscher and Pennartz, 2008). In brief, DU posits that a decision maker behaves as if she maximized discounted utility, with discounted utility being the sum of the discount-factor-weighted utilities of all possible final states. Classically, DU assumed an exponentially decreasing discount function with a constant discount rate (**Figure 2A**; Samuelson, 1937). Constant discounting has important implications for rationality and time-consistency of preference. According to DU, it is not irrational or non-optimal *per se* to prefer small, short-term over large, long-term rewards, even if the preference for immediacy results in an overall reduced net gain over time. However, DU requires *consistency* over time. That is, if an individual prefers a small, short-term reward over a large, long-term reward, and both rewards are shifted in time by

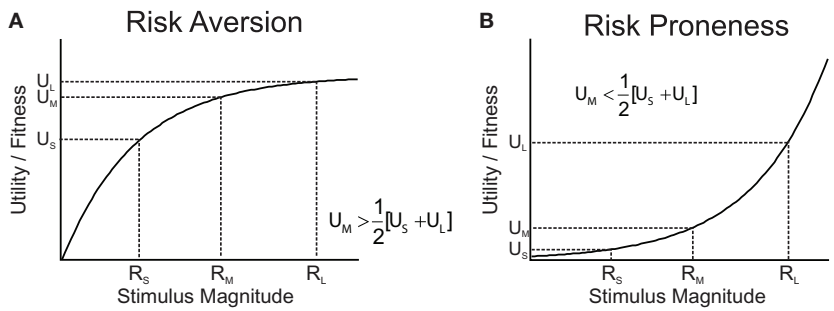

FIGURE 1 | Utility functions can explain risk attitude according to expected utility theory and risk sensitivity theory. (A) Utility (for humans) or Darwinian fitness (for animals) as a function of the magnitude of a commodity. The utility/fitness curve is concave and is a decelerating function of the current level of stimulus magnitude (wealth/amount) because the marginal utility/fitness increment decreases with increasing level of stimulus magnitude. A concave utility/fitness function predicts risk aversion when choosing between a medium-sized, certain reward (R_M) and a risky option offering large or small rewards (R_S and R_L) with equal probabilities. **(B)** A convex function predicts risk proneness.

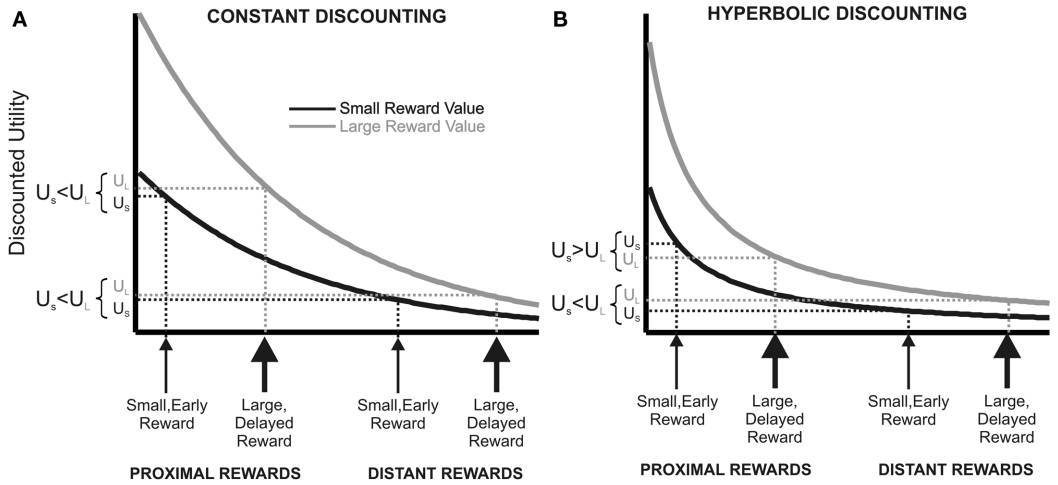

FIGURE 2 | Constant vs. hyperbolic discounting of future events. The figure describes a choice between a small, short-term outcome or a large, long-term outcome (proximal), and another situation in which both outcomes are deferred into the future by the same time interval (distant). **(A)** Constant (here: exponential) utility function of a large, delayed (gray line) and small, short-term commodity (black line). With exponential discounting, preference stationarity holds when the rewards are deferred by the same time interval into the future. **(B)** People seem to place a premium on short-term availability of rewards, deflecting the discount into an upward direction for temporally close rewards. The resulting hyperbolic discount function can explain preference reversals over time. Due to the steeper utility decay for short delays, the utility of the small, short-term commodity is higher than the large, delayed reward for temporally proximal outcomes, but the utility order reverses when both outcomes are deferred into the future.

an identical time interval, then the preference for the small, short-term reward should be preserved because both rewards should be discounted by the same rate.

Animals also make decisions over time: during foraging, several time delays affect the rate of energy gain, for instance travel time between food patches, handling time of an item of prey, time between unsuccessful and successful foraging attempts etc. Behavioral ecologists assumed that animals maximizing Darwinian fitness should use foraging strategies that maximize, in the long run, the net energy gain per time unit, i.e., the ratio of food intake to the time needed to obtain or consume the food (Stephens and Krebs, 1986). For example, in a choice between large, delayed and small, short-term rewards, rate maximization predicts that animals prefer large rewards when the ratio of reward amount per time unit is higher for the large than for the small reward.

The reinforcement learning literature in psychology made predictions regarding animal and human decision making over time that are comparable to the predictions of rate maximization in biology. Thorndike's (1911) *law of effect*, stating that "responses that produce a satisfying effect in a particular situation become more likely to occur again in that situation" implies that greater reinforcement (more frequent, bigger, or more preferred rewards) results in greater response rates (more frequent behaviors that produce the reward). This has led to formulation of the *matching law* (Herrnstein, 1961, 1970), according to which the relative selection-rate of one out of several choice options matches the relative rate of reinforcement offered by that option. Hence, the shorter the time intervals between rewards, the higher the reward rate, the more often the option offering these rewards should be chosen. In other words, as predicted by optimal foraging models, animals obeying the matching law would maximize energy gain rate in choice situations where the different choice alternatives yield different streams of reward rates (Kalenscher et al., 2003).

SIMILARITIES AND DIFFERENCES BETWEEN ECONOMIC, BIOLOGICAL, AND PSYCHOLOGICAL MODELS OF CHOICE BEHAVIOR

The previous paragraph shows that, even though rate maximization is a prescriptive, normatively flavored theory and the matching law is a descriptive, empirically derived model, both approaches make very similar predictions. However, the similarities between rate maximization and DU are less apparent, and their correspondence is also less evident than for EU and risk sensitivity theory in decision making under risk. In fact, the differences between the two approaches seem more obvious at first glance than their similarities. For instance, DU and optimal foraging theory differ in that DU makes no prediction about the optimality of preferring small, short-term or large, long-term rewards, whereas optimal foraging theory predicts that animals should maximize long-term reward rate. On the other hand, whereas DU prescribes time-consistent preferences when adding a constant time interval to all rewards optimal foraging may predict preference reversals[2]. Nevertheless, despite these differences, both theories have remarkable similarities, too. Both approaches are normative and prescribe rather than

[2]Assume an animal chooses between (a) two food items delivered after 2 s (rate: one item per second) and, (b), four food items delivered after 8 s (rate: 1/2 items per second; hence a > b). If both rewards were delayed by 10 s, the energy rate for option (a′) would change to 0.17 items per second and for option (b′) to 0.22 items per second. Optimal foraging theory predicts preference for a over b, but b′ over a′; DU prescribes consistent preference because of constant discounting, i.e., a over b and a′ over b′. Note that the rate maximization model can be modified to match DU, for instance by assuming a non-linear value function linking Darwinian fitness to energy gain.

describe optimal behavior. They both assume maximization of a currency (utility in DU and energy rate in optimal foraging theory). Also, they have in common that they condemn a disproportionally strong, impulsive preference for immediacy as non-optimal if it leads to discontinuous preferences over time (see Frederick et al., 2002; Kalenscher and Pennartz, 2008; Kalenscher and Tobler, 2008 for review, but see Stephens and Anderson, 2001; Stephens et al., 2004). Hence, despite the disparity of the two approaches, both frameworks would agree on the classification of a large range of different strategies as rational or as anomalous.

In summary, despite considerable differences, the normative literature in economics and ecology on choice behavior of human and non-human animals, and some of the descriptive literature in psychology, makes remarkably similar assertions and predictions about decision making under risk and over time. Presumably the most notable difference between choice theories in economics, ecology, and psychology is the focus (or lack of it) on cognitive processes. Whereas theories in economics often explicitly refrain from making any statements about the choice-underlying cognitive processes, and emphasize their pure focus on outcome instead (in many, if not most economic models, a decision maker behaves *as if* she maximized EU; (Samuelson, 1938; Gul and Pesendorfer, 2005), theories in cognitive psychology do precisely the opposite, i.e., put the spotlight on process, but not outcome. Note, though, that the sub-discipline in psychology that has the strongest tradition in using animal subjects, behaviorism, shares with economics the strict rejection of investigating mental process. Behaviorists are interested in describing stimulus–response or response–outcome relationships, and explicitly refuse to make any statements about the cognitive "black box" that links stimulus with outcome. Biological theories are less strict in their distinction between process and outcome, and, whereas some ecological theories have a more exclusive emphasis on one or the other, other theories combine process and outcome (e.g., Reboreda and Kacelnik, 1991; Bateson and Kacelnik, 1996; see Kacelnik, 2006 for review).

THE REALITY OF DECISION MAKING: HUMANS AND ANIMALS SHOW VERY SIMILAR VIOLATIONS OF ECONOMIC THEORY

The previous paragraphs suggested that the difference in human and animal economic behavior is much smaller than one may think at first glance. This notion is corroborated by several lines of research that empirically test predictions of economic theory using non-human animals, including monkeys, rats, and pigeons (see e.g., Kagel et al., 1975, 1981, 1995; MacDonald et al., 1991; Santos and Keith Chen, 2009). These studies show that rats, for instance, comply surprisingly well to the predictions of demand theory, price theory, labor supply, decision making under risk and intertemporal choice. Yet, despite the accuracy of economic theory to account for much of human and animal behavior, we know from personal experience and countless publications in the literature on decision making that humans often fail to meet the strict assumptions made in classic economic models. Interestingly, many, if not most of the violations of the predictions of economic theory that can be observed in humans are also found in animals. The next paragraph gives a brief and selective overview of some of these violations.

In contradiction to the common assumption of unconditional self-interest (discussed, for instance, in Fehr and Fischbacher, 2002), most human individuals do care about the well-being of others, either in a *prosocial* way by, e.g., giving to charity or accepting costs to improve the well-being of others, or in a counter-utilitaristic way, e.g., in parochial situations where the well-being of others is reduced at a cost and without direct benefit to the actor (Fehr and Schmidt, 1999; Fehr and Fischbacher, 2002, 2003; Camerer, 2003; Baron, in press). Moreover, humans are able to cooperate with a partner even if defection would satisfy their material self-interest better in the short run (Trivers, 1971; Rilling et al., 2002). In addition to strategic considerations, such as reputation building, genuine social motives like inequity aversion and envy presumably play a role during social behavior (Fehr and Schmidt, 1999). Despite strong controversy (see, for instance, Henrich, 2004; Wynne, 2004a, b), animal behavior seems to some extent be guided by social motives, too. For instance, capuchin monkeys appear to be inequity averse (Brosnan and De Waal, 2003), and capuchin monkeys (de Waal et al., 2008), tamarins (Hauser et al., 2003), chimpanzees (de Waal and Suchak, 2010; Melis et al., 2011), rats (Rutte and Taborsky, 2007, 2008), fish (Raihani et al., 2010), and various other animals, including insects (Axelrod and Hamilton, 1981) show behavior resembling direct or generalized reciprocity. Not only great apes and monkeys (de Waal and Suchak, 2010), but also blue jays (Stephens et al., 2002), rats (Viana et al., 2010), fish (Raihani et al., 2010), and many social insects, like bees and ants (Kolmer and Heinze, 2000; Ratnieks and Helantera, 2009; Rueppell et al., 2010), cooperate with conspecifics in social situations; social insects even accept high costs, such as sacrificing their own life, if this benefits the society (Ratnieks and Helantera, 2009; Rueppell et al., 2010).

Economic models make inadequate assumptions and predictions in non-social contexts, too. For instance, the notions of internal consistency and stable preferences are often violated: human subjects frequently show *intransitive preferences*, preferring choice alternative A over B and B over C, but not A over C (Tversky, 1969; Kalenscher and Pennartz, 2010; Kalenscher et al., 2010), or make *context-dependent* choices, preferring A over B, but reversing this preference when an inferior option C is added to the pool of choice alternatives (also known as a violation of the independence axiom; Tversky and Simonson, 1993). Intransitive and context-dependent choices can occur when individuals choose between alternatives that vary along several dimensions, e.g., gain magnitude and probability. People seem to fail to treat each multidimensional option as an integrated whole, but appear to compare each attribute separately and then consider the difference between attributes instead of the difference between utilities attributes[3] (Tversky, 1969; Roelofsma and Read, 2000; Brandstätter et al., 2006; Kalenscher and Pennartz, 2010; Kalenscher et al., 2010). Many animals reveal inconsistent preferences, too, even when internal homeostatic drives, such as hunger or thirst, are controlled for: honeybees, pigeons, and gray jays show intransitive preferences (Navarick and Fantino, 1972,

[3]For example, assume a decision maker chooses between three gambles: (A) win \$40 with probability $p = 0.4$, (B) win \$45 with $p = 0.35$, and (C) win \$50 with $p = 0.3$. This individual may consider the difference in probability between gambles A and B (Δp) = 0.05) too small to care about, and consequently chooses the gamble with the higher gain magnitude [Δ(gain) = \$5], hence A > B. The same logic applies to choices between B and C, hence B > C. However, the difference in probability between A and C [(Δp) = 0.1] may exceed a cognitive "threshold," and, because of the participant's risk aversion, she may choose the safer gamble with the higher probability, hence C > A.

1975; Shafir, 1994; Waite, 2001), and hummingbirds show violations of the independence axiom and make context-dependent decisions (Bateson et al., 2003).

Choices are particularly prone to inconsistency when making decisions over time. It has been repeatedly shown that preferences reverse when the delays to both rewards are advanced or deferred in time, and basically a discontinuity of preference can often be observed when immediate outcomes become available[4] (*time-inconsistent preferences*; Thaler and Shefrin, 1981; Benzion et al., 1989; Ainslie and Haslam, 1992; Green et al., 1994; Kirby and Herrnstein, 1995; Frederick et al., 2002; Kalenscher and Pennartz, 2008; Kalenscher and Tobler, 2008). Such non-stationarity of intertemporal preferences suggests that people add extra value to short-term availability of rewards (illustrated in **Figure 2B**). The disproportionally high value placed on short-term rewards is believed to be responsible for the fact that most humans find it very difficult to act in accordance with their long-term interest (Haynes, 2009). Examples include breaking diets, living unhealthy lifestyles, financial illiteracy, insufficient retirement provisions, substance abuse and even mundane issues like postponing dentist appointments. The inadequacy of DU to account for the reality of intertemporal choice behavior is even more apparent when dealing with delayed losses or aversive events. DU did not make a particular distinction between the treatment of losses and gains: the aversiveness of losses should be discounted as much as the attractiveness of gains when the outcome of a decision is more and more delayed. However, it has been shown that the attractiveness of gains is reduced faster than the aversiveness of losses (Thaler and Shefrin, 1981), implying a different discount rate for gains than for losses. An even greater challenge for DU is the observation that many human subjects prefer to expedite a loss instead of delaying it. If losses loom less when they are temporally remote, as predicted by DU, subjects should be ready to defer losses into the future. However, many subjects actually prefer to incur a loss or an aversive event immediately rather than delay it (Loewenstein, 1987; Benzion et al., 1989). Much like humans, a whole range of different animals, including monkeys, pigeons, rats, mice, and even insects show non-stationary, time-inconsistent intertemporal choices in tasks involving front-end delay (i.e., adding a common time interval to both options), and place extra value on instant outcomes (Rachlin and Green, 1972; Ainslie, 1974, 1975; Green et al., 1981; Bateson and Kacelnik, 1996; Kacelnik, 1997; Isles et al., 2003; Kalenscher et al., 2005, 2006a; Kalenscher and Pennartz, 2008; Kim et al., 2008; Louie and Glimcher, 2010). When choosing between timed aversive events, rats, much like humans, sometimes accelerate, rather than defer electric shocks (Knapp et al., 1959).

Some violations of economic theory are less intuitive than time-inconsistent preferences. Even though according to EU or other classic economic models, risk attitudes should be consistent when making decisions under risk, individuals prefer certain options when gambling for gains, but risky options when gambling to avoid losses (Kahneman and Tversky, 1979). This reversal of risk attitude has been termed the *reflection effect* because the reflection of the prospects around 0 (changing the sign from gains to losses) reverses the preference order. Reflection effects suggest that, apparently, choices are not made with respect to final states, but with respect to changes in final states, i.e., with respect to gains and losses. Risk attitude and the reflection effect are not only functions of objective gains and losses, but the way a problem is (verbally) presented affects the way it is cognitively treated (Kahneman and Tversky, 1979, 1984). For example, the choice of words can influence whether one and the same prospect is perceived as a choice between gains, or as a choice between losses. Such *framing* of a decision problem has an effect on the subjects' risk attitude and determines whether she is risk-averse (for gains) or risk-prone (for losses). Moreover, humans show a strong overweighting of rare events, and a literal discontinuity in preference when certain outcomes become available (certainty effect; Kahneman and Tversky, 1979). Rats and various birds also show reflection effects and reversals of risk attitudes (Kacelnik and Bateson, 1996; Bateson and Kacelnik, 1998), and rats (MacDonald et al., 1991) and honeybees (Shafir et al., 2008) show certainty effects. Moreover, starlings show framing effects when making decisions under risk: they reverse their risk preference depending on whether the relative reward levels in a risky condition are higher or lower than the reward level in a standard "frame" (Marsh and Kacelnik, 2002). Another violation of economic theory includes the *sunk-cost fallacy* – the continued investment of money, time, effort, or resources into an unsuccessful project over a long period of time although the project clearly yields no results, and an investment into an alternative activity would promise better outcomes (Kogut, 1990; Arkes and Ayton, 1999). Pigeons commit the sunk-cost fallacy, too: their persistence to respond on a pecking key in an expected ratio schedule in which a probabilistic reward is delivered if a fixed ratio performance (a fixed number of responses) with variable response frequency requirements is met, is strongly influenced by their previous effort investment on that key (Navarro and Fantino, 2005). Finally, the *endowment effect* refers to the observation that goods that are in possession of a subject seem to be valued higher by the subject than goods that can be purchased (Grether and Plott, 1979). Endowment effects can be found in chimpanzees, too (Brosnan et al., 2007).

Note that the existence of these violations does not falsify EU or other economic or biological theories; it merely implies that economic theory does not apply to people (or animals) who do not meet the rationality assumptions posited by economic theory (Samuelson, 1938). However, it is of crucial interest for economists and biologists alike to understand *why* animals and humans so frequently and systematically violate economic or ecological theory. Only animal research offers the opportunity to use invasive tools, and thus manipulate cognitive mechanisms and their neural substrates to study the effect on economic behavior. Importantly, therefore, investigation of animal choices and their neural substrates in carefully translated experimental paradigms could yield data on the neural implementation of decision parameters that would otherwise be hard to obtain. These data should ultimately be used to update existing models of human brain function in economic decisions.

HOW CAN ANIMAL MODELS INFORM ECONOMIC RESEARCH?

ANIMAL BEHAVIOR OFFERS INSIGHT INTO THE EVOLUTIONARY ROOTS OF DECISION MAKING

Of course, one of the foremost reasons to use animals in decision research is methodological, as briefly touched upon in the introduction. Neuroeconomics aims to reveal the neural processes underlying

[4]For example, when given the choice between receiving $10 today, or $20 in a year, many individuals prefer $10 today. If both options were shifted into the future by, say, 50 years (now the choice is between $10 in 50 years and $20 in 51 years), most individuals would prefer the more delayed $20.

economic decision making. The majority of the most accurate and promising technologies used in neuroscience research cannot be used on humans for ethical and practical reasons, including basic manipulations such as lesion studies, electrophysiology, microdialysis, psychopharmacology and others. As trivial as it is to point out, animal models are therefore an indispensible and crucial tool in neuroeconomic research. However, we hope to have convinced the reader by now that methodological reasons are not the only grounds to use animal subjects for studying economic decision making.

In the previous chapters, we have emphasized the parallels in the theoretical models on human and animal decision making and pointed up the correspondence in actual economic behavior. The similarities in compliance with and violations of the predictions of economic theory suggest that some rudiments of human decision patterns can also be found in non-human animals. This implies that human and animal decision making may share evolutionary roots: presumably, the way we make decisions today is the result of natural selection, so that the choice mechanisms found in modern humans probably once (and maybe still today) equipped decision makers in the best possible way to adapt to and deal with the intricacies of the environments in which they evolved. This offers unique insights into the sense or nonsense of violating optimality principles, such as variable and time-inconsistent preferences.

Several authors argue that, although the decision rules used by modern humans provided the highest possible fitness increases to animals in the environments in which they evolved, they may actually be maladaptive today and fail to perform well in the intricate and flexible environmental structure of modern societies (Kahneman and Tversky, 1996). Take the example of time-inconsistent intertemporal choices: Stephens (2002, 2008) maintains that the short-sighted, over-impulsive decision mechanisms observed in animals when making intertemporal decisions are actually well adapted to meet the challenges an animal is facing in a real environment. An animal's real environment does, for example, have a sequential foreground/background structure. Sequential means that decisions are usually not between binary options (choose either A *or* B, which is usually the case in laboratory experiments), but between a sequence of options, such as the decision whether to stay in a currently exploited, depleting food patch or leave to another food patch (which involves traveling time/effort and the risk of not finding an equivalent one), or whether to attack a prey item or continue searching for better prey. Foreground/background means that an animal usually follows a default strategy (background: searching for food) that needs to be put on hold for the time being if a potential food item is encountered (foreground). Several authors (Stephens and Anderson, 2001; Stephens, 2002, 2008) have shown that animals making non-optimal decisions in artificial laboratory situations actually choose optimally in economically equivalent, but sequential foreground/background choice situations that meet the criteria of higher ecological validity. Hence, the very same choice rules that perform well in these "natural" choice scenarios, produce deviations from normative models, such as impulsive, delay-oversensitive preferences in artificial laboratory settings. If the choice mechanisms humans employ to make intertemporal decisions share common evolutionary roots with non-human animals, then natural selection has favored decision rules that are optimally adapted to the sequential foreground/background environment of foraging animals, but the same decision rules may fail to perform well in our "modern" binary-choice environments where over-impulsiveness is a vice, not a virtue.

In contrast to the view that violations of normative ideals are maladaptive, others (Gigerenzer and Goldstein, 1996; Goldstein and Gigerenzer, 2002; Hutchinson and Gigerenzer, 2005; Brandstätter et al., 2006) maintain that human decision rules are as adaptive now as they were when they evolved because the benefits of these rules, such as computational speed and accuracy, outweighed the drawbacks, such as the occasional non-optimal choice, back then as much as now. According to this view, comparative research yields optimality criteria that were previously not recognized or considered in traditional economic models (Hutchinson and Gigerenzer, 2005). Comparative research may thus contribute to modifying and amending existing normative theories to improve their descriptive validity and explanatory power. For example, a decision maker who maximized expected utility for decision making under risk should behave as if she integrated each outcome's probability with the utility of the outcome, and compared these integrated utilities across outcomes. Such a computation involves several mental transformations: translation of objective reward magnitude into utility, multiplication with an accurate mental representation of probability, repeating this for every option, and comparing these integrated expected utilities across options. Several authors argued that the direct comparison of the attributes, i.e., comparing probabilities and reward magnitudes separately, provides in most cases a much more accurate, fast, precise, easy, and less error-prone estimation of the best option than the "economically sound" way, albeit at the cost of making inconsistent choices in special circumstances (Russo and Dosher, 1983). It has been argued that such decision rules evolved because they maximized Darwinian fitness in animals (Houston, 1997) and prevail because they continue to produce near-optimal decision outcomes in humans, too (Russo and Dosher, 1983; Brandstätter et al., 2006).

However, identifying the evolutionary basis of choice behavior is not the only reason to conduct animal research on economic decision making. The analysis of animal behavior is a convenient, economical, and sound way to test competing economic decision models in optimally controlled experimental environments. The cultural, cognitive and motivational confounds and the experimental design issues related to differences in belief- and value-systems that are very difficult to overcome in human research are not an issue in animal studies. Moreover, animal models allow for experimental manipulations, including real appetitive and aversive consequences, that are for practical and ethical reasons not implementable in human research. As pointed out by Kagel et al. (1995), animals are a mean to probe the elementary principles of microeconomic theory: if these basic principles fail to account for the behavior of simple organisms, such as rats or pigeons, in simple choice situations, such as Skinner box experiments, how can they be trusted in much more complex situations involving much more complex organisms, such as our worldwide economic systems with human actors? Or, in other words, "[…] a theory that works well across species has a greater likelihood of being valid than one that works will with only one, or a limited set of, species." (Kagel et al., 1995, p. 4).

Economic research on animals is often criticized on the grounds that animals are considered irrational and instinct-driven. Hence, how could economic theory that relies on the assumption of

rational decision makers be applied to animal behavior? In addition to the problematic usage of the word "instinct," we hope to have conveyed the message that the differences in animal and human behavior and cognition may be a matter of degree, and not of kind, as testified by the remarkable conformity of animal decision making with the principles of microeconomic theory (Kagel et al., 1995), and also with the parallels between human and animal behavior in violating them.

In sum, we argue that neither pure theoretical reasoning nor exclusive experimentation with human subjects will be sufficient to obtain a comprehensive picture of human decision making, including where humans conform to the principles of rational choice models and where and why humans violate them. We maintain that, in order to understand not only how we make decisions, but also to investigate *why* our decisions are what they are, it is imperative to know the reserve constraints, evolutionary pressures, and adaptive benefits that molded the choice behavior in the first place, aiming to add construct validity to the models. We conclude that the prime way to obtain access to the evolutionary pressures shaping our decision mechanisms and to identify common denominators in choice behavior is to study animal behavior and its neural mechanisms.

CAUTION IS REQUIRED WHEN DRAWING PARALLELS BETWEEN HUMAN AND ANIMAL BEHAVIOR

In the previous paragraphs, we have emphasized the parallels in the theoretical models on human and animal decision making and pointed up the similarities in economic behavior. Admittedly, we conveniently skipped the discussion of the differences in theories and behavior. However, if we want to use animal models to explain human behavior, it is imperative to know not only the similarities, but also the differences across species. Moreover, it is dangerous to draw cross-species parallels in behavior and mechanism too quickly since many findings may have face validity only. That is, because a problem can be solved by a plethora of different mechanisms, it is quite possible that human and animal economic choice behavior, and many of the violations of rational choice observed across species, appear similar and are therefore given identical names, while the underlying cognitive and neural processes may be fundamentally different. Even though this is less of a predicament for traditional economics given that economics is conventionally only interested in prescribing choice–outcome relations, not in identifying the choice-underyling mental and neural processes, this is particularly problematic for disciplines interested in those very processes, including cognitive psychology, comparative biology, and neuroscience. Therefore, much of comparative research aims to identify which mental processes are comparable across species, and which ones are not (Rosati et al., 2007).

Moreover, as the previous paragraphs illustrated, caution is even more warranted when drawing parallels between human and animal economic behavior since the experimental designs used may bias results and their interpretation. For obvious reasons, the procedures and designs used to elicit the behaviors in humans and animals described in the preceding paragraphs have several fundamental differences. The most evident difference lies in the incentivization used to motivate human and animal participants: whereas humans are usually paid contingent on their choices or are instructed to imagine virtual payoffs, animals receive food or liquid rewards. Food and money are essentially dissimilar commodities: whereas food is a primary reward (eliciting a strong direct hedonic response), money is a powerful secondary reinforcer (money itself does not produce a hedonic response, only its association with primary reinforcers makes it a reward). This calls into question in how far the results of comparative intertemporal choice experiments are commensurable. Moreover, during intertemporal choice studies, the delays associated with money in human studies are usually in the range of months or years, whereas the delays associated with food rewards in animal studies are usually in the range of seconds. Even though one may dismiss comparative human and animal research as non-commensurable in principle based on these grounds, recent attempts in the intertemporal choice literature to match the experimental procedures used in humans to the ones common in animal research suggest the opposite. The incentives used in these studies involved primary rewards, such as liquids (McClure et al., 2007) and pictures of the opposite sex (Hayden et al., 2007) and involved much shorter delays. The results show that human participants exhibited the same behavioral patterns found with secondary reinforcers, such as money. Moreover, the neural networks involved in making intertemporal decisions for primary rewards, with delays in the seconds to minutes range, were remarkably similar to the networks involved in financial intertemporal decisions with delays in the range of days to months (McClure et al., 2004, 2007). The procedure-independence of behavior and neural mechanism suggests that the agreement of intertemporal choice behavior in animals and humans cannot easily be dismissed based on procedural grounds alone. In partial support of this, in an experimental design that was manufactured to allow best-possible comparison between species, Rosati et al. (2007) showed that humans were generally only as delay-tolerant, and often even slightly *less* patient than chimpanzees and bonobos when waiting for future primary rewards. Because of the parallel in delay tolerance between humans and apes, and since the degree of patience exhibited by the apes exceeded the level predicted by common short-term maximization models, the authors conclude that the capacity to endure long delays for food evolved before the human lineage split, suggesting that apes and humans share common intertemporal choice mechanisms, at least for primary rewards. However, because humans were substantially more patient to wait for monetary rewards, they also suggested that the human ability to delay gratification for secondary reinforcers is unprecedented in the animal kingdom, raising doubts about whether the mental processes for primary and secondary rewards are identical. Nevertheless, given the indications discussed above, the overall evidence implies that the procedural differences in studies using primary and secondary reinforcers, and the mental processes involved, may be less significant than feared.

Also in the domain of decision making under risk, there are elementary differences in the typical procedures used in animal and human research. In humans, subjects are usually instructed about the probabilities of a gain or a loss, often in one-shot scenarios (only one question asked, no repetitions). By contrast, because animals cannot be verbally instructed, reward probabilities are usually operationalized as reward frequencies in multi-trial settings, so that a reward with a probability of 0.8 implies that, on average, 8 out of 10 trials are rewarded. It is likely that extracting reward probabilities from reward frequencies involves fundamentally different

cognitive and neural systems than when being instructed about these attributes in one-shot sessions. Moreover, several authors pointed out that tasks involving probabilistic rewards may *not* be interpreted by the animal subject as a decision under risk, but as an intertemporal choice (Rachlin et al., 1986; Hayden and Platt, 2007; Kalenscher, 2007). According to this idea, it is possible that reward frequencies are construed as delays so that, for instance, a reward with a probability of 0.5 is perceived as a reward with a delay of, on average, two trials duration. However, here again, several lines of evidence suggest that procedural differences are not necessarily a blackout argument to dismiss any belief in a similarity between human and animal decision making under risk. For instance, some behavioral patterns in human behavior that are found when probabilities are instructed can also be found when probabilities have to be extracted from reward frequencies. For example, in a study touched upon above, Fantino and Navarro found that humans and pigeons were equally likely to commit the sunk-cost fallacy in a task in which the (human and avian) participants had to decide whether to persist to respond in an expected ratio schedule, or abort a trial and start a new one (Navarro and Fantino, 2005). By contrast, others argue that probabilities extracted from experience induce different behavioral biases than instructed probabilities (Hertwig et al., 2004). For instance, the typical overweighting of rare events when probabilities are instructed (Kahneman and Tversky, 1979) contrasts with a characteristic underweighting of low likelihoods when probabilities are extracted from experience (Hertwig et al., 2004). However, comparative research with bees and humans suggest that this divergence of evidence between descriptive and experience-based likelihood extraction can be attributed to perceptual noise when extracting information from experience, and the original overweighting, in both bees and humans, can be reinstated when perceptual noise is reduced (Shafir et al., 2008). This would suggest, again, that procedural differences are less significant than feared. However, another study found that preference reversals (here: the tendency to *place higher value* on a high risk, high magnitude gamble, but to *prefer* a low risk, low magnitude gamble) are reduced when human subjects extract probabilities from experience, and not from description (Chu and Chu, 1990).

In conclusion, it is still under debate whether animal models for decision under risk are suitable approximations of human decision making, given the controversy whether the mental processes involved when extracting probability information from experience or instruction are identical. Nevertheless, at least some evidence suggests that animals and humans behave similarly when procedural differences are controlled for, implying, but not proving, that the underlying choice mechanisms may be similar, too. We want to stress that this uncertainty is by no means reducing the necessity of animal research. On the contrary, because parallels in brain functioning cannot always straightforwardly be drawn between humans and animals at large, but also between different species of animals and their diverging brain connectivity involved in choice behavior, exactly those differences between species can be highly informative and can shed light on the function of the underlying systems. For example, the conclusion that the cognitive and neural mechanisms underlying intertemporal choice are identical across species is not always straightforwardly supported by the empirical reality: because activity in human ventral striatum is often positively correlated with impulsiveness, present-bias, or with choices of the most temporally proximal option, as revealed by functional magnetic resonance imaging (Hariri et al., 2006; Glimcher et al., 2007; Kable and Glimcher, 2007), one would expect that less ventral striatum activity would predict more delay tolerance. However, the opposite has been found in animal research: rats with lesioned ventral striatum are more, not less impulsive, compared to control rats (Cardinal et al., 2001), suggesting that the integrity of ventral striatum is necessary for maintaining self-control (in the sense of delay-tolerance). Even though it is impossible to entirely rule out that the ventral striatum plays a functionally different role in rats and humans during intertemporal choice, this explanation is unlikely because the ventral striatum is phylogenetically identical and homologous across species (Reiner et al., 1984; Pennartz et al., 1994; Durstewitz et al., 1999; Mezey and Csillag, 2002; Izawa et al., 2003). It is more likely that the ventral striatum plays a role in optimizing decisions over time, according to which too much or too little ventral striatal activity results in suboptimal, impulsive decisions. This idea is supported by a wealth of findings in the psychopharmacology literature suggesting that both amplifying and antagonizing the dopaminergic input into the ventral striatum increases impulsiveness in rats and humans (Evenden and Ryan, 1996; Cardinal et al., 2000; Cardinal, 2006; Boettiger et al., 2007; Buckholtz et al., 2010; Pine et al., 2010). We conclude from this example that comparative research provides better answers to the question of the role of ventral striatum in intertemporal choice than research with either species alone. Hence, what is needed is a comprehensive comparative approach, preferably across humans and multiple species of non-human animals, in which lab studies on animal and human economic decision making are additionally complemented by field studies to probe the theories in real-world environments.

CONCLUSION

In this perspective review, we have argued that, even though the contexts wherein economic decisions made by humans on the one hand and animals on the other can be vastly different, economic theory can be remarkably successfully applied to human *and* animal behavior alike. We regard the critical examination of economic theory the prime objective of performing experiments in decision making and we maintain that in this light it is imperative to include animal models in the arsenal at our disposal. In the worst case, results obtained in animals will corroborate those obtained from humans, strengthening the existing theory. Preferably, though, comparative research will uncover inconsistencies in choice behavior between humans and animals that allow for an improved, more comprehensive description of choice behavior and possibly force us to re-think the basis of economic theory in the light of the evolutionary roots of choice.

A potential problem using this approach remains that results obtained with human and animal choice paradigms could have only face validity in reproducing each others' findings, and could diverge in the underlying cognitive processes subserving economic decision making. Rather than viewing this as a discredit to comparative research, we see underconstrainment of the cognitive processes governing choice behavior as an invitation to bridge the fields of biology, psychology and economics in further, careful probing of the neural basis of economics decision making across species.

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Scarce means with alternative uses: Robbins' definition of economics and its extension to the behavioral and neurobiological study of animal decision making

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Almost 80 years ago, Lionel Robbins proposed a highly influential definition of the subject matter of economics: the allocation of scarce means that have alternative ends. Robbins confined his definition to human behavior, and he strove to separate economics from the natural sciences in general and from psychology in particular. Nonetheless, I extend his definition to the behavior of non-human animals, rooting my account in psychological processes and their neural underpinnings. Some historical developments are reviewed that render such a view more plausible today than would have been the case in Robbins' time. To illustrate a neuroeconomic perspective on decision making in non-human animals, I discuss research on the rewarding effect of electrical brain stimulation. Central to this discussion is an empirically based, functional/computational model of how the subjective intensity of the electrical reward is computed and combined with subjective costs so as to determine the allocation of time to the pursuit of reward. Some successes achieved by applying the model are discussed, along with limitations, and evidence is presented regarding the roles played by several different neural populations in processes posited by the model. I present a rationale for marshaling convergent experimental methods to ground psychological and computational processes in the activity of identified neural populations, and I discuss the strengths, weaknesses, and complementarity of the individual approaches. I then sketch some recent developments that hold great promise for advancing our understanding of structure–function relationships in neuroscience in general and in the neuroeconomic study of decision making in particular.

Keywords: behavioral economics, neuroeconomics, decision making, opportunity cost, psychophysics, reward, brain stimulation, dopamine

ROBBINS' DEFINITION

In his landmark essay on the nature of economics, Lionel Robbins defined economics as

> "the science which studies human behaviour as a relationship between ends and scarce means which have alternative uses" (Robbins, 1935, p. 16).

At first glance, this formulation seems a dry and inauspicious note on which to launch a discussion of the behavioral and neurobiological study of economic decision making in animals. Robbins' definition confines economics to the study of human behavior, he sought to distinguish economics from the natural sciences, and he firmly opposed attempts to "vivisect the economic agent" (Maas, 2009).

Why then, use his definition as a starting point? I do so because deletion of a single word, "human," frees the core idea underlying Robbins' definition to apply as broadly and fundamentally in the domain of animal biology as in the originally envisaged domain of human economic behavior. Robbins opined:

> "The material means of achieving ends are limited. We have been turned out of Paradise. We have neither eternal life nor unlimited means of gratification. Everywhere we turn, if we choose one thing we must relinquish others which, in different circumstances, we wish not to have relinquished. Scarcity of means to satisfy ends of varying importance is an almost ubiquitous condition of human behaviour" (Robbins, 1935, p. 15).

This statement is no less true of the behavior of non-human animals.

Robbins' definition is highly general and is not restricted to exchanges such as barter or market transactions. To illustrate the point that even "isolated man" engages in economic behavior, Robbins (1935, pp. 34–35) describes a choice facing Robinson Crusoe, the castaway protagonist of the eponymous classic novel (Defoe, 1719/2010). Crusoe is marooned on a tropical island. A decision making challenge faced by this solitary individual is positioned by Robbins firmly within the economic realm:

> "Let us consider, for instance, the behaviour of a Robinson Crusoe in regard to a stock of wood of strictly limited dimensions. Robinson has not sufficient wood for all the purposes to which he could put it. For the time being the stock is irreplaceable. [. . .] if he wants the wood for more than one purpose – if, in addition to wanting it for a fire, he needs it for

> fencing the ground round the cabin and keeping the fence in good condition – then, inevitably, he is confronted by a [. . .] problem – the problem of how much wood to use for fires and how much for fencing."

Let us now ponder another example, one that illustrates both the boundary Robbins draws between non-economic and economic behavior and how readily his definition can be transposed to the behavior of non-human animals.

SCARCE MEANS WITH ALTERNATIVE USES

Consider the case of a diving duck incubating eggs in a shoreline nest. In this terrestrial environment oxygen is abundant. Breathing can be performed at the same time as other activities, such as preening, incubating the eggs, and scanning for predators. The duck need not forgo engagement in other behaviors in order to devote time to the exchange of oxygen and carbon dioxide. If we extend Robbins' definition to the circumstances of the nesting duck, we will see that no economic principles govern breathing in this environment and that no allocation decisions need be made to ensure the necessary gas exchange.

Now consider the same duck as it forages for fish. Entry into the aquatic environment renders oxygen a scarce good. According to my extension of Robbins' definition, the duck's quest for oxygen has moved into the economic realm. In the aquatic environment, oxygen, in a form exploitable by the duck, is available only at the surface whereas prey are found only in the depths. Two vital ends, gas exchange and energy balance, are now in conflict. The time available for attainment of each of these ends is scarce, and it has alternative uses. The duck can fish or breathe, but it cannot do both at the same time or in the same place. To maximize its rate of energy intake, the duck must draw down its precious supply of oxygen, traveling to the attainable locations where prey densities are highest and harvesting what it can while it is able to remain there. Maximization of net energy intake thus trades off against conservation of sufficient blood oxygen for a safe return to the surface. The duck must remain there long enough to at least partially replenish its oxygen supply. However, if it consistently lingers too long at the surface, it will starve, and if it tarries too long submerged, it will drown.

Many means of survival in the natural world are scarce or tend toward this condition. Consider a population that moves into a new environment where food is initially abundant. All else held equal, the population will grow, increasing demand for food while decreasing supply. Abundance will be fleeting and self-limiting.

The trade-off between breathing and feeding in aquatic animals has been modeled by behavioral ecologists using principles that are economic, in the spirit of Robbins' definition, and that reflect the optimal allocation of scarce means with alternative uses (Kramer, 1988). In the case of the diving duck, such an optimal-foraging model predicts how variation in the depth and density of prey alter how the duck distributes its time between the surface and the underwater environment. More generally, such models predict how animals allocate their time in the pursuit of spatially constrained ("patchy") resources. Time is the quintessentially scarce resource, a view Robbins expressed as follows:

> "Here we are, sentient creatures with bundles of desires and aspirations, with masses of instinctive tendencies all urging us in different ways to action. But the time in which these tendencies can be expressed is limited. The external world does not offer full opportunities for their complete achievement. Life is short" (Robbins, 1935, pp. 12–13).

As the duck runs down its oxygen supply on a deep dive that has yet to yield any fish, the scarcity of time makes itself evident with particular force.

Later in this essay, I speculate about what Robbins meant by "sentient," and I argue that sentience is not a necessary condition for economic behavior. I discuss the implications of extending Robbins' definition into the biological realm, and I describe an experimental paradigm for the laboratory study of economic decision making in non-human animals that is based on the allocation of time as a scarce resource.

THE CONTRIBUTION OF PSYCHOPHYSICS TO VALUATION

Allocation decision are based on information about the external world, such as distributions of predators and prey, and about the internal environment, such as the state of energy and oxygen stores. These exteroceptive and interoceptive data are acquired, processed, and stored by sensory, perceptual, and mnemonic mechanisms whose dynamic range, resolution, and bandwidth are limited by physics, anatomy, and physiology. Veridical representation of the external world is unfeasible.

Psychophysics describes how objective variables, such as luminance, are mapped into their subjective equivalents, such as brightness. Such mappings are typically non-linear and reference-dependent. Non-linearity is exemplified by the Weber–Fechner law (Weber, 1834/1965; Fechner, 1860, 1965), which posits that the smallest perceptual increment in a stimulus is a constant proportion of the starting value. Such logarithmic compression sacrifices accuracy as stimulus strength grows but makes efficient use of a finite dynamic range. Reference dependence is illustrated by demonstrations that the important information conveyed by the visual system does not concern luminance *per se* but rather relative differences in luminance with respect to the mean (i.e., contrast). This feature can be advantageous. Consider a checkerboard made of alternating dark-gray and light-gray squares. The objective property of the squares that causes them to look dark or light is called "reflectance," and the corresponding subjective quality is called "lightness." If perception were dependent only on the processing of local information according to the Weber–Fechner law, then increasing the intensity of the illumination impinging on the checkerboard would, in illusory fashion, drive the percept of the lighter squares toward white and the percept of the dark-gray squares toward a lighter gray. However, the contrast between adjoining squares remains constant as objective luminance increases. (By definition, contrast is normalized by the mean luminance.) Thus, we perceive the lightness of each kind of square as constant over a wide range of luminance.

In the example of the checkerboard, reference dependence helps the visual system recover a meaningful property of an object in the world, the relative reflectances of its components, factoring out the change in viewing conditions. However, reference dependence can

also cause the subjective lightness of a region under constant illumination to vary as a function of changes in the illumination of the surrounding region (simultaneous lightness contrast). In that case, perhaps an unusual one in the natural environment, reference dependence leads to a perceptual error. Thus, a mechanism that normally serves to recover facts about the world can also produce illusions.

Whereas sensory systems provide information about the location, identity, and displacement of objects in the external world, valuation systems estimate what these objects are worth. Valuation systems provide the data for allocation decisions. The neural systems subserving valuation cannot put back information that has been filtered out by their sensory input, and these systems have information-processing constraints, rules, and objectives of their own. Thus, a realistic model of allocation decisions must take into account the psychophysical functions that map objective variables into subjective valuations. As we will see shortly, the mappings of variables involved in valuation also tend to be non-linear and reference-dependent. They, too, embody built-in rules of thumb that are usually beneficial but that can sometimes generate systematic errors.

Below, I describe a particular model in which psychophysical transformations contribute to the allocation of a scarce resource, and I illustrate how the form of these transformations can be used strategically to link stages in the processes of valuation and allocation to specific neural populations. But first, we must respond to Robbins' objections to consideration of psychophysics in economic decision making.

DID ROBBINS PROTEST IN VAIN?

Prominent nineteenth century economists, such as Jevons (1871/1965) and Edgeworth (1879), incorporated psychophysical concepts into their theories of valuation (Bruni and Sugden, 2007). For example, the Weber–Fechner law (Weber, 1834/1965; Fechner, 1860, 1965) was used to interpret the law of diminishing returns (Bernoulli, 1738, 1954), the notion that the subjective value of cumulative increments in wealth decreases progressively. Although the practice of incorporating psychophysics into economics was commonplace in the late nineteenth century, it was all but abandoned under the influence of a later generation of economists led by Pareto (1892–1893/1982, as cited in Bruni and Sugden, 2007) and Weber (1908), who sought to purge economics of psychological notions and to treat the principles of choice as axiomatic (Bruni and Sugden, 2007; Maas, 2009).

By the second edition of his landmark essay, Robbins had acknowledged that the foundations of valuation are "psychical," but he treated such matters as beyond the scope of economics:

> "Why the human animal attaches particular values [. . .] to particular things, is a question which we do not discuss. That is quite properly a question for psychologists or perhaps even physiologists. All that we need to assume as economists is the obvious fact that different possibilities offer different incentives, and that these incentives can be arranged in order of their intensity" (Robbins, 1935, p. 86).

Robbins shared the firm opposition of Pareto and Weber to basing an economic theory of subjective value on psychophysics, and he also endorsed with their strong conviction that "the fundamental propositions of microeconomic theory are deductions from the assumption that individuals act on consistent preferences" (Sugden, 2009). He saw this assumption as self-evident and thus exempt from the need for experimental validation (Sugden, 2009).

Under Robbins' influence and that of contemporary economic luminaries, such as Hicks and Allen (1934), and Samuelson (1938, 1948), the theory, and subject matter of psychology was all but banished from the economic mainstream by the middle of the twentieth century (Laibson and Zeckhauser, 1998; Bruni and Sugden, 2007; Angner and Loewenstein, in press). The psychophysical notions entertained by the nineteenth century economists came to be regarded as unnecessary to the economic enterprise because powerful, general theories could be derived without them based on assumptions that seemed irrefutable (Bruni and Sugden, 2007).

The exile of psychology from economics was not to last. At least a partial return has been driven by developments in the psychology of decision making and by the related emergence of behavioral economics as an important and influential sub-discipline (Camerer and Loewenstein, 2004; Angner and Loewenstein, in press). The behavioral economic program seeks to base models of the economic agent on realistic, empirically verified psychological principles. Crucial to this approach are challenges to notions that Robbins, Weber, and Pareto took to be self-evident (Bruni and Sugden, 2007; Sugden, 2009), such as the consistency and transitivity of preferences (Tversky, 1969; Tversky and Thaler, 1990; Hsee et al., 1999). The *Homo psychologicus* who emerges from behavioral economic research uses an array of cognitive and affective shortcuts to navigate an uncertain, fluid world in real time. These shortcuts generate systematic behavioral tendencies that are economically consequential. *Homo psychologicus* is more complex than the *Homo economicus* erected by the neoclassical economists, more challenging to model, but more recognizable among the people we know and observe.

Kahneman and Tversky's work on heuristics and biases (Tversky and Kahneman, 1974), and on prospect theory (Kahneman and Tversky, 1979; Tversky and Kahneman, 1992), is seen to have brought behavioral economics into the economic mainstream (Laibson and Zeckhauser, 1998). Heuristics are simple rules of thumb that facilitate decision making by helping an economic agent avoid the paralysis of indecision and keep up with a rapidly evolving flow of events (Gigerenzer and Goldstein, 1996; Gilovich et al., 2002; Gigerenzer and Gaissmaier, 2011). One line of research on heuristics highlights the ways in which heuristics improve decision making (Gigerenzer and Goldstein, 1996; Gigerenzer and Gaissmaier, 2011). Another illustrates how shortcuts that ease the computational burden may sometimes do so at the cost of generating errors that *Homo economicus* would not make (Tversky and Kahneman, 1974; Kahneman and Tversky, 1996). Because these errors are not random, they lead to predictable biases in decision making.

Prospect theory (Kahneman and Tversky, 1979) provides a formal framework for integrating heuristics and mapping functions analogous to psychophysical transformations. Prospects, such as a pair of gambles, are first "framed" in terms of gains or losses. This imposes reference dependence at the outset by establishing the current asset position as the point of comparison. The position

of this "anchor" can be displaced by verbal reformulations of a prospect that do not change its quantitative expectation, e.g., by casting a given prospect as a loss with respect to a higher reference point as opposed to a gain with respect to a lower one. Two mapping functions are proposed, one that transforms gains and losses into subjective values and a second that transforms objective probabilities into decision weights (which operate much like subjective probabilities). The outputs are multiplied so as to assign an overall value to a prospect. Like common psychophysical transformations, the mapping functions are non-linear. The shape of the value function not only captures the law of diminishing returns (Bernoulli, 1738, 1954), it is also asymmetric, departing more steeply from the origin in the realm of losses than in the realm of gains. This asymmetry makes predictions about changes in risk appetites when a prospect is framed as a loss rather than as a gain or vice-versa. The decision-weight function is bowed, capturing our tendency to overweight very low-probability outcomes, to assign an inordinately high weight to certain outcomes, and to underweight intermediate probabilities.

Prospect theory argues that the form and parameters of the non-linear functions mapping objective variables into subjective ones are consequential for decision making. On this view, the choices made by the economic agent can neither be predicted accurately nor understood without reference to such mappings. Thus, prospect theory and related proposals restore psychological principles of valuation to a central position in portrayals of the economic agent.

Below, I point out some analogies between prospect theory and a model that links time allocation by laboratory rats to benefits and costs (Arvanitogiannis and Shizgal, 2008; Hernandez et al., 2010). Although they advocate caution when drawing parallels between decision making in humans and non-human animals, Kalenscher and van Wingerden (2011) detail many cases in which departures from the axioms of rational choice, discovered by psychologists and behavioral economists in their studies of humans, are mirrored in the behavior of laboratory animals. Of particular relevance to this essay is their discussion of the work of Stephens (2008) showing how a rule that can generate optimal behavior in the natural environment can produce time-inconsistent preferences in laboratory testing paradigms. This is reminiscent of how simplifying rules that prove highly serviceable to our sensory systems in natural circumstances can generate perceptual illusions under laboratory conditions.

VIVISECTING THE ECONOMIC AGENT

Since Robbins published his seminal essay almost 80 years ago, at least four intellectual, scientific, and technological revolutions have transformed the landscape in which battles about the nature of the economic agent are fought. The cognitive revolution, which erupted in force in the 1960s, overthrew the hegemony of the behaviorists (labeled a "queer cult" by Robbins), restored internal psychological states as legitimate objects of scientific study, and provided rigorous inferential tools for probing such states. A later revolt, propelled forward by Zajonc's (1980) memorable essay on preferences, reinstated emotion as a major determinant of decisions and focused much subsequent work on the interaction of cognitive and affective processes (LeDoux, 1996; Metcalfe and Mischel, 1999; Slovic et al., 2002a,b). Meanwhile, progress in neuroscience has vastly expanded what we know about the properties of neurons and neural circuitry while generating an array of new tools for probing brain–behavior relationships at multiple levels of analysis. Finally, we now find ourselves surrounded by "intelligent machines" with capabilities that would likely have astounded Robbins. These computational devices have expanded common conceptions of what can be achieved in the absence of sentience.

Robbins strove to isolate economics from dependence on psychological theory. Thus, it is not surprising that his essay on the nature and significance of economics provides only a few indications of his views regarding the qualities of mind required of the economic agent. One of these is the ability to establish a consistent preference ordering. The use of such an ordering to direct purposive behavior is discussed as requiring time and attention, which suggests that he had in mind a deliberative process, the working of which the individual is aware. Robbins also refers to us as "sentient beings." Webster's II New Riverside University Dictionary (Soukhanov, 1984) defines "sentient" as "1. Capable of feeling: CONSCIOUS. 2. Experiencing sensation or feeling." The definition of "purposive" provided by The Collins English Dictionary (Butterfield, 2003) includes the following: "1. relating to, having, or indicating conscious intention." We cannot be sure exactly which meanings he intended, but Robbins' text suggests to this reader that experienced feelings, deliberation and conscious intent were linked in his conception of what is required for the purposive pursuit of ends and the allocation of scarce means to achieve them.

Since Robbins wrote his essay, thinking about the role of experienced feelings, deliberation and conscious intent in decision making and purposive behavior has evolved considerably. A highly influential view (Fodor, 1983) links the enormous computational abilities of our brains to the parallel operation of multiple specialized modules that enable us to perform feats such as the extraction of stable percepts from the constantly changing flow of sensory information, construction of spatial maps of our environment, transformation of the babble of speech sounds into meaningful utterances, near-instantaneous recognition of thousands of faces, etc. Most of the processing subserving cognition, the workings of the specialized modules, is seen to occur below the waterline of awareness. The conscious processor is portrayed as serial in nature, narrowly limited in bandwidth by a very scarce cognitive resource: the capacity of working memory (Baddeley, 1992). Thus, conscious processing constitutes a formidable processing bottleneck, and it is reserved for applications of a special, integrative kind (Nisbett and Wilson, 1977; LeDoux, 1996; Baars, 1997; Metcalfe and Mischel, 1999).

The resurgence of interest in emotion has brought affective processing within the scope of phenomena addressed by a highly parallel, modularized computational architecture. In Zajonc's (1980) view, evaluative responses such as liking or disliking emerge spontaneously and precede conscious recognition – they arise from fast processes operating in parallel to the machinery of cognition, as traditionally understood. Indeed, the cognitive apparatus often busies itself with the development of plausible after-the-fact rationalizations for unconscious affective responses of which it is eventually informed. Zajonc's ideas have contributed to a dual view of

decision making in which deliberative and emotional processes vie for control (Loewenstein, 1996; Metcalfe and Mischel, 1999; Slovic et al., 2002a,b). Deliberative processing entails reasoning, assessment of logic and evidence, and abstract encoding of information in symbols, words, and numbers; it operates slowly and is oriented toward actions that may lie far off in the future. In contrast, emotional processing operates more quickly and automatically; it is oriented toward imminent action. Under time pressure or when decisions are highly charged, the affective processor is at an advantage and is well equipped to gain the upper hand. Particularly important to the dual-process view is its emphasis on operations that take place outside the scope of consciousness thoughts and experienced feelings, i.e., beyond sentience. Unlike what I am guessing Robbins to have assumed, the dual-process view allows both cognitive and affective processing to influence decision making without necessarily breaching the threshold of awareness.

It has long been recognized that we share with non-human animals many of the rudiments of affective processing (Darwin, 1872). In parallel, much evidence has accumulated since Robbins' time that non-human animals have impressive cognitive abilities, including the creation of novel tools (Whiten et al., 1999; Weir et al., 2002; Wimpenny et al., 2011) and the ability to plan for the future (Clayton et al., 2003; Correia et al., 2007). Thus, both the reintegration of emotion into cognitive science and new developments in the study of comparative cognition add force to the notion that basic processes underlying our economic decisions also operate in other animals. I leave aside the question of the degree to which sentience should be attributed to various animals, but I note that the continuing development of artificial computational agents has expanded our sense of what is possible in the absence of consciousness thoughts and experienced feelings. For example, reinforcement-learning algorithms equip machines with the ability to build models of the external world based on their interaction with it and to select and pursue goals with apparent purpose (Sutton and Barto, 1998; Dayan and Daw, 2008; Dayan, 2009).

Developments since Robbins' time have not only lent momentum to the behavioral economic program, they have also motivated initiatives to further "vivisect the economic agent" by rooting it in neuroscience. Twenty-five years ago, a presentation on decision making would have evoked puzzlement and no small measure of disapproval at a neuroscientific conference; now, such conferences are far too short to allow participants to take in all the new findings on this topic of burgeoning interest. The emergence of computational neuroscience as an important sub-field has provided a mathematical lingua franca and a mutually accessible frame of reference for communication between scholars in neuroscience, decision science, computer science, and economics.

The neuroeconomic program (Glimcher, 2003; Camerer et al., 2005; Glimcher et al., 2008; Loewenstein et al., 2008) seeks to replace *Homo psychologicus* with *Homo neuropsychologicus*. This program offers the hope that internal states hidden to behavioral observation can be monitored by neuroscientific means and, particularly in laboratory animals, can be manipulated so as to support causal inferences. The spirit of the neuroeconomic initiative shares much with that of the behavioral economic program, which is also concerned with what is "going on inside" the economic agent. However, the neuroeconomist draws particular inspiration from the striking successes achieved in fields such as molecular biology, where our understanding of function has been expanded profoundly by discoveries about structure and mechanism.

AN EXPERIMENTAL PARADIGM FOR THE BEHAVIORAL, COMPUTATIONAL, AND NEUROBIOLOGICAL STUDY OF ALLOCATION UNDER SCARCITY

A neuroeconomic perspective has informed several different experimental paradigms for the study of decision making in non-human animals (Glimcher, 2003; Glimcher et al., 2005, 2008; Kalenscher and van Wingerden, 2011). One of these entails pursuit of rewarding electrical brain stimulation (Shizgal, 1997). In the following sections, I describe a variant of this paradigm (Breton et al., 2009; Hernandez et al., 2010), which I relate to Robbins' definition of economics. At the end of this essay, I sketch a path from this particular way of studying animal decision making to broader issues in neuroeconomics.

Rats, and many other animals, will work vigorously to trigger electrical stimulation of brain sites arrayed along the neuraxis, from rostral regions of prefrontal cortex to the nucleus of the solitary tract in the caudal brainstem. The effect of the stimulation that the animal seeks, called "brain stimulation reward (BSR)", can be strikingly powerful and can entice subjects to cross electrified grids, gallop an uphill course obstructed with hurdles, or forgo freely available food to the point of starvation. Although the stimulation makes no known contribution to the satisfaction of physiological needs, the animals act as if BSR were highly beneficial, and they will work to the point of exhaustion in order to procure the stimulation.

Adaptive allocation of scarce behavioral resources requires that benefits and costs be assessed and combined so as to provide a result that can serve as a proxy for enhancement of fitness. The electrical stimulation that is so ardently pursued appears to inject a meaningful signal into neural circuitry involved in computing the value of goal objects and activities. For example, the rewarding effect produced by electrical stimulation of the medial forebrain bundle (MFB) can compete with, summate with, and substitute for the rewarding effects produced by natural goal objects, such as sucrose and saline solutions (Green and Rachlin, 1991; Conover and Shizgal, 1994; Conover et al., 1994). This implies that the artificial stimulation and the gustatory stimuli share some common attribute that permits combinatorial operations and ultimate evaluation in a common currency.

My coworkers and I have likened the intensity dimension of BSR to the dimension along which the reward arising from a tastant varies as a function of its concentration (Conover and Shizgal, 1994; Hernandez et al., 2010). On this view, a rat that works harder for an intense electrical reward than for a weaker one is like a forager that pursues a fully ripe fruit more ardently than a partially ripe one. Both are relinquishing a goal they would have sought under other circumstances for a different goal that surpasses it in value. Viewed in this way, the subjective intensity dimension is fundamental to economic decision making, as defined in the broad manner advocated here.

In many experiments on intracranial self-stimulation (ICSS), the cost column of the ledger is manipulated by altering the

contingency between delivery of the rewarding stimulation and a response, such as lever pressing. Conover and I have developed schedules of reinforcement that treat time as a scarce resource in the sense of Robbins' definition (Conover and Shizgal, 2005; Breton et al., 2009). Like the human economic agents portrayed by Robbins, our rats have "masses of instinctive tendencies" urging them "in different ways to action." Even in the barren confines of an operant test chamber, rats will engage in activities, such as exploration, grooming, and resting, that are incompatible with the actions required to harvest the electrical reward. One of our schedules imposes a well controlled opportunity cost on the electrical reward (Breton et al., 2009). (The opportunity cost is the value of the alternate activities that must be forgone to obtain the experimenter-controlled reward.) On this schedule, the rat must "punch a clock" so as to accumulate sufficient work time to "get paid." This is accomplished by delivering the stimulation once the cumulative time the rat has held down a lever reaches the criterion we have set, which we dub the "price" of the reward. We use the term "cumulative handling-time" to label this schedule. (In behavioral ecology, handling-time refers to the period during which a prey item is first rendered edible, e.g., by opening a shell, and then consumed.) To paraphrase Robbins, the conditions of the cumulative handling-time schedule require that if the rat chooses to engage in one activity, such as holding down the lever, it must relinquish others, such as grooming, exploring, or resting, which, in different circumstances (e.g., in the absence of BSR), it would not have relinquished. Like stimulation strength, price acts as an economic variable, as defined in the broad manner advocated here.

The key to making time a scarce resource is to ensure the exclusivity of the different activities in which the rat might engage. An exception illustrates the rule. In an early test of our cumulative handling-time schedule, a rat was seen to turn its back to the lever, hold it down with its shoulder blades, and simultaneously groom its face. By repositioning the lever, we were able to dissuade this ingenious fellow from defeating our intentions, and none of our rats have been seen since to adopt such a sly means of rendering their time less scarce.

Traditional schedules of reinforcement (Ferster and Skinner, 1957) do not enforce stringent time allocation. Interval schedules control when rewards are available, but little time need be devoted to operant responding in order to harvest most of the rewards on offer; the subject can engage in considerable "leisure" activity without forgoing many rewards. Ratio schedules do control effort costs, but they leave open the option of trading off opportunity costs against the additional effort entailed in responding at a higher cadence. In contrast, the cumulative handling-time schedule enforces a strict partition of time between work and leisure.

ALLOCATION OF TIME TO THE PURSUIT OF REWARDING ELECTRICAL BRAIN SIMULATION

Figure 1A illustrates how rats allocate their time while working for BSR on the cumulative handling-time schedule. We define an experimental trial as a time interval during which the price and strength of the electrical reward are held constant. The trial duration is made proportional to the price, and thus, a rat that works incessantly will accumulate a fixed number of rewards per trial. The ordinate of **Figure 1A** plots the proportion of trial time ("time allocation") spent working for the electrical stimulation. When the price of BSR is low, the rat forgoes leisure activities and spends almost all its time holding down the lever to earn electrical rewards. As the price is increased, the rat re-allocates the scarce resource (its time), engaging more in leisure activities and less in work. **Figure 1B** illustrates what happens when the price of the electrical reward is held constant but its strength is varied. The stimulation consists of a train of current pulses; under the conditions in force when the data in **Figure 1** were collected, each pulse is expected to have triggered an action potential in the directly activated neurons that give rise to the rewarding effect (Forgie and Shizgal, 1993; Simmons and Gallistel, 1994; Solomon et al., 2007). Thus, the higher the frequency at which pulses are delivered during a train, the more intense the neural response, and the more time is allocated to pursuit of BSR. **Figures 1C,D** are two views of the same data, which were obtained by varying both the pulse frequency and the price; the high-frequency stimulation trains were cheap whereas the low-frequency ones were expensive.

Figure 2A combines the data shown in **Figure 1** in a three-dimensional (3D) depiction. We call the surface that was fit to the data points (depicted by the black mesh in **Figure 2A** and the colored curves in **Figure 1**) the "reward mountain." **Figure 2B** summarizes the data in **Figure 2A** in a contour map. To obtain this map, the reward mountain is sectioned horizontally at regular intervals and the resulting profiles plotted as black lines; the gray level represents the altitude (time allocation). The shape of the reward mountain reflects the intuitive principle that the rat will allocate all or most of its time to pursuit of stimulation that is strong and cheap but will allocate less for stimulation that is weak and/or expensive.

A FUNCTIONAL/COMPUTATIONAL MODEL

Figure 1 shows that the allocation of a scarce behavioral resource, the time available to obtain BSR, is tightly and systematically controlled by two objective economic variables: the strength (pulse frequency) and opportunity cost (price) of a stimulation train. **Figure 3** depicts a empirically based model (Arvanitogiannis and Shizgal, 2008; Hernandez et al., 2010) of why the data in **Figures 1** and **2** assume the form they do. Each component is assigned a specific role in processing the signal injected by the electrode and in translating it into an observable behavioral output. The mathematical form of each transformation is specified, and simulations can thus reveal whether the model can or cannot reproduce the dependence of the rat's behavior on the strength and cost of the reward. The correspondence of the fitted surface to the data hints that it can. Insofar as the model specifies psychological processes involved in economic decisions, the model is positioned within the behavioral-economic tradition, and insofar as at least some of its components are couched in terms of neural activity, it is also has a neuroeconomic flavor.

Let us consider first the core of the model, the memory vector in the center of the schema at the top of **Figure 3**. The elements of this vector are subjective values. Thus, the top and bottom elements are simply the subjective mapping of stimulation strength and opportunity cost. The remaining two elements represent the

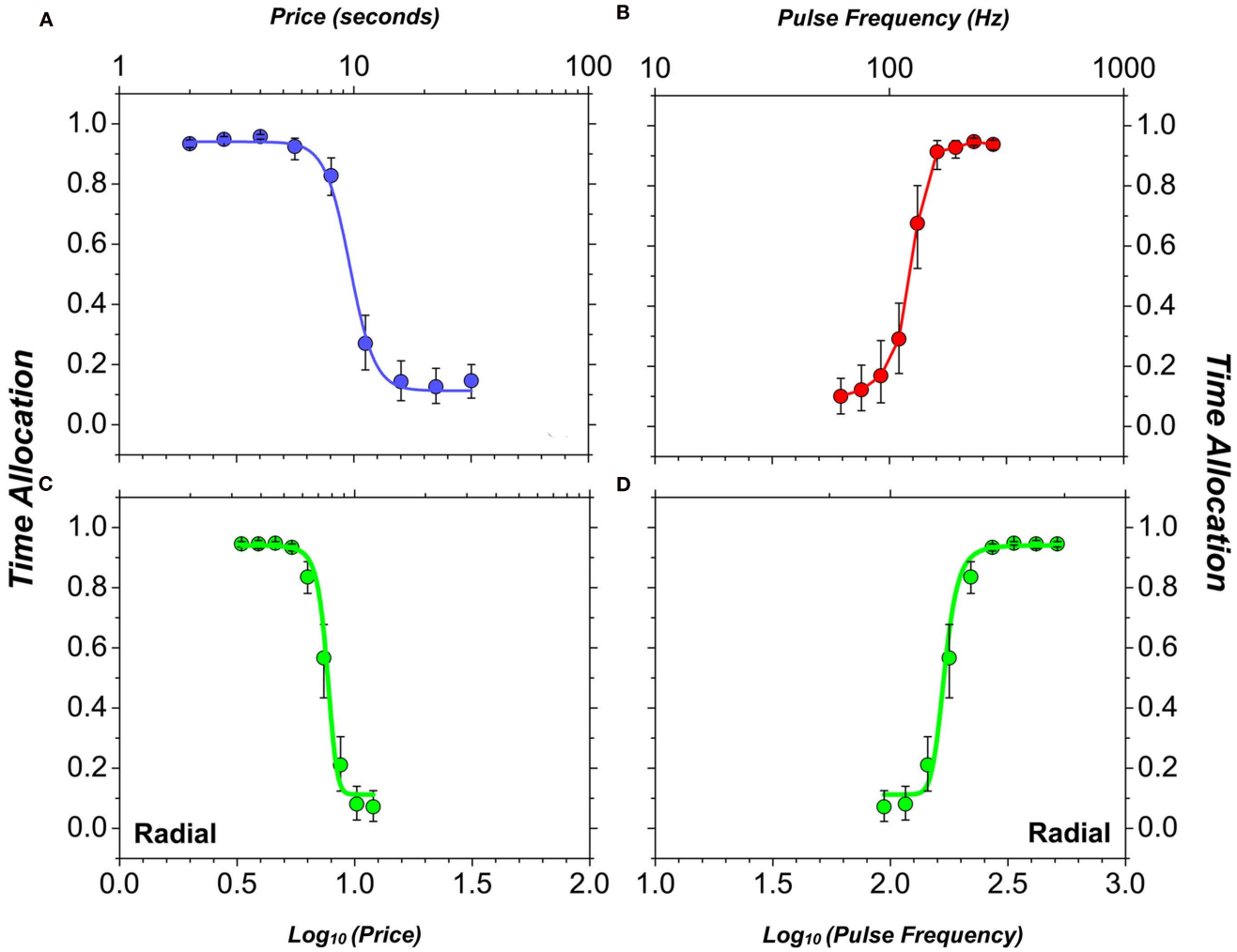

FIGURE 1 | Sample data (Hernandez et al., 2010) showing how the strength (pulse frequency) and price (opportunity cost) of electrical stimulation trains influence the proportion of the rat's time devoted to seeking out the electrical reward. (A) time allocation to pursuit of trains of different opportunity cost with reward strength held constant; **(B)** time allocation to pursuit of trains of different strength with opportunity cost held constant; **(C)** time allocation to pursuit of trains with inversely correlated strength and opportunity cost (strong trains are cheap, weak ones are expensive), plotted as function of opportunity cost; **(D)** time allocation to pursuit of trains with inversely correlated strength and opportunity cost (strong trains are cheap, weak ones are expensive), plotted as function of strength. Smooth curves are projections of the surface fitted to the data (shown in **Figure 2A**).

subjective estimate of the probability of receiving a reward upon satisfaction of the response requirement and the physical exertion required to hold down the lever. The values in the memory vector are combined in a manner consistent with generalizations (Baum and Rachlin, 1969; Killeen, 1972; Miller, 1976) of Herrnstein's matching law (Herrnstein, 1970, 1974): The subjective reward intensity is scaled by the subjective probability and by the product of the subjective effort and opportunity costs. We refer to the result of this scalar combination as the "payoff" from pursuit of BSR.

Note the analogy between this model and prospect theory. In both cases, non-linear functions map objective economic variables into subjective ones, and the results are combined in scalar fashion. In both cases, the form and parameters of the mapping functions matter. Changing either can alter the ranking of a given option in the subject's preference ordering.

To translate the payoffs obtained by scalar combination of the quantities in the memory vector into observable behavior, an adaptation (Hernandez et al., 2010) of McDowell's (2005) single-operant version of the generalized matching law is employed. This expression relates the animal's allocation of time to the relative payoffs from work and leisure. With the payoff from BSR held constant, time allocated to work decreases in sigmoidal fashion as the payoff from leisure activity grows (green curve in the 3D box at the right of **Figure 3**). Similarly, with the payoff from leisure activities fixed, time allocated to pursuit of a BSR train increases sigmoidally with the payoff from the stimulation (purple curve in the 3D box at the right of **Figure 3**).

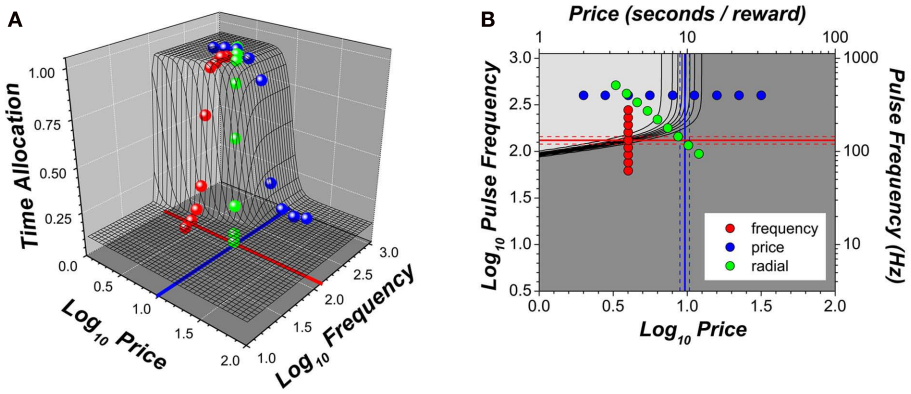

FIGURE 2 | Three-dimensional views of the data in Figure 1. (A) Scatter plot of data means along the with surface fitted to the data; **(B)** contour plot of the fitted surface and the sampled pulse frequencies and prices. The solid red line represents the position parameter of the intensity-growth function: the pulse frequency that produces a reward of half-maximal intensity. This parameter determines the position of the three-dimensional structure along the pulse frequency axis. The solid blue line represents the price at which time allocated to pursuit of a maximal reward falls half-way between its minimal and maximal values; this parameter determines the position of the three-dimensional structure along the price axis. Dashed lines represent 95% confidence intervals.

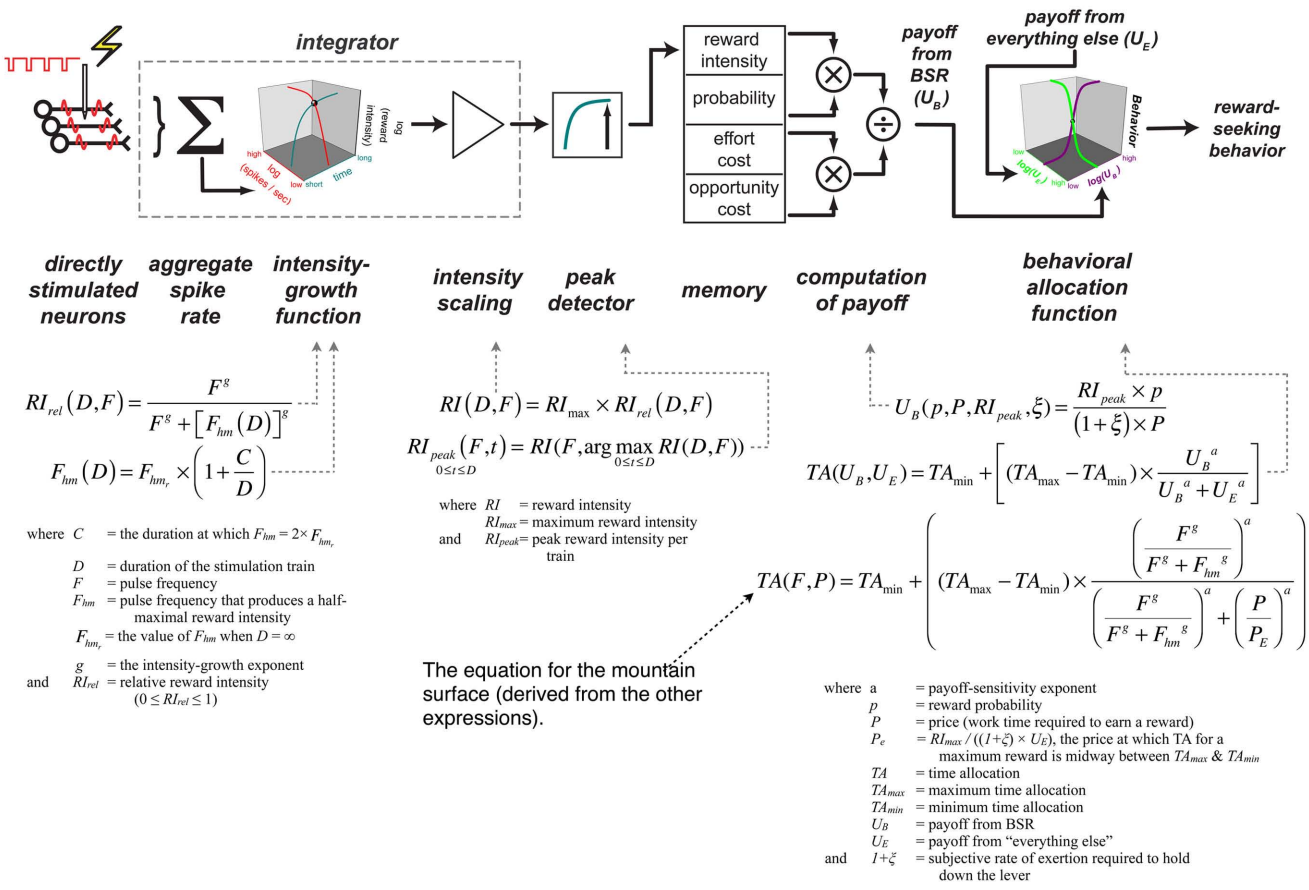

FIGURE 3 | A functional/computational model of how time allocated to reward seeking is determined by the strength and cost the reward (Hernandez et al., 2010). The derivation of the expressions and their empirical basis is provided in the cited paper.

The left portion of **Figure 3** describes how the parameters of the pulse train are mapped into the subjective intensity of the rewarding effect. Several stages of processing are shown, including one of the four psychophysical functions that generate the values

stored in the memory vector. The schema at the left represents the inference that over a wide range of frequencies, each pulse triggers a volley of action potentials in the directly stimulated neurons responsible for the rewarding effect (Gallistel, 1978; Gallistel et al., 1981; Forgie and Shizgal, 1993; Simmons and Gallistel, 1994; Solomon et al., 2007). The synaptic output of these neurons is integrated spatially and temporally and transformed by an intensity-growth function. In accord with experimental data (Leon and Gallistel, 1992; Simmons and Gallistel, 1994; Arvanitogiannis and Shizgal, 2008; Hernandez et al., 2010), the red curve in the 3D box on the left of **Figure 3** shows that reward intensity grows as a logistic function of the aggregate firing rate produced by a stimulation train of fixed duration, and the cyan curve depicts the growth of reward intensity over time in response to a train of fixed strength (Sonnenschein et al., 2003). The scaled output of the intensity-growth function is passed through a peak detector en route to memory: it is the maximum intensity achieved that is recorded (Sonnenschein et al., 2003).

Not shown in **Figure 3** are the three remaining psychophysical functions, the ones responsible for mapping reward probability, exertion of effort, and opportunity cost into their subjective equivalents. **Figure 4** presents the prediction of Mazur's hyperbolic temporal discounting model (Mazur, 1987) as applied to the psychophysical transformation of opportunity cost; the plotted curves are based on data from a study of delay discounting in ICSS (Mazur et al., 1987). Ongoing research (Solomon et al., 2007) is assessing the relative merits of the Mazur model and several alternatives as

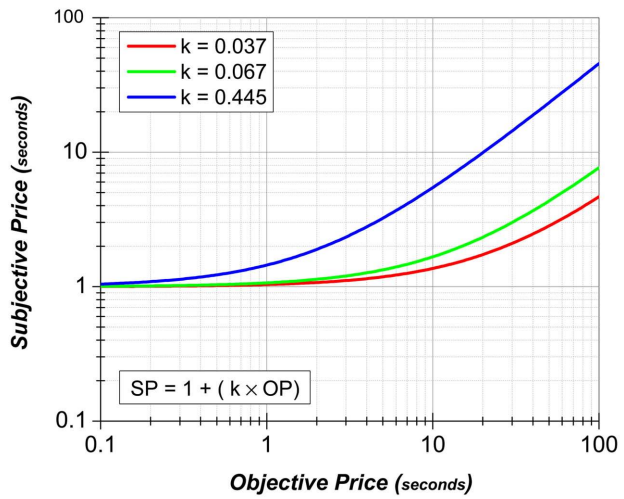

FIGURE 4 | Mazur's hyperbolic delay-discount function (Mazur, 1987), replotted as a subjective-price function. The price is the cumulative time the rat must hold down the lever in order to earn a reward. Thus, from the perspective of the Mazur model, the price is couched as a delay to reward receipt, and the subjective-price is inversely related to the discounted value. The value of the reward at zero delay has been set arbitrarily to one. The delay-discount constants (Mazur's k) for the plotted curves are derived from a study by Mazur et al. (1987); the red curve represents the value for subject 1, the green curve for subject 2, and the blue curve for subject 3. Alternative models of the subjective-price function are under ongoing investigation (Solomon et al., 2007).

accounts of the impact of opportunity costs on performance for BSR. The subjective probability and effort–cost functions have yet to be described.

The contours in **Figure 2B** trace out the intensity-growth function (Hernandez et al., 2010). The non-linear form of this function makes it possible to discern in what direction the mountain surface described by these contours has been displaced by experimental manipulation of the reward circuitry. **Figure 5** shows how the mountain is shifted by treatments acting at different stages of the model. Interventions in the early stages, prior to the output of the intensity-growth function, displace the mountain along the axis representing the strength of the rewarding stimulation (pink surface). In contrast, interventions in later stages displace the mountain along the axis representing the cost of the rewarding stimulation (blue surface). Consequently, the reward mountain can be used to narrow down the stages of processing at which manipulations such as drug administration, lesions, or physiological deprivation act to alter reward seeking. Conventional two-dimensional measurements are not up to this task: identical displacements of psychometric curves, such as the ones shown in **Figure 1**, can be produced by shifting the 3D reward mountain in orthogonal directions (Hernandez et al., 2010; Trujillo-Pisanty et al., 2011).

In early work on the role of dopamine neurons in BSR, the changes in reward pursuit produced by manipulation of dopaminergic neurotransmission were attributed to alterations in reward intensity (Crow, 1970; Esposito et al., 1978). However, cocaine, a drug that boosts dopaminergic neurotransmission, displaces the 3D reward mountain rightward along the price axis (Hernandez et al., 2010). This links the drug-induced change in dopamine signaling to a later stage of processing than was originally proposed, one beyond the output of the intensity-growth function. Among the actions of cocaine that are consistent with its effect on the position of the mountain are an upward rescaling of reward intensity (Hernandez et al., 2010) and a decrease in subjective effort costs (Salamone et al., 1997, 2005). Blockade of the CB-1 cannabinoid receptor also displaces the mountain along the price axis, but in the opposite direction to the shift produced by cocaine (Trujillo-Pisanty et al., 2011). These effects of perturbing dopamine and cannabinoid signaling illustrate why it is important to learn the form of psychophysical valuation functions, to measure them unambiguously, and to take into account multiple variables that contribute to valuation.

LIMITATIONS OF THE MODEL

The model in **Figures 3** and **5** has fared well in initial validation experiments (Arvanitogiannis and Shizgal, 2008) and has also provided novel interpretations of the effects on pursuit of BSR produced by pharmacological treatments (Hernandez et al., 2010; Trujillo-Pisanty et al., 2011). That said, it important to acknowledge that the current instantiation is a mere way station en route to a challenging dual goal: a fully fleshed out description of the neural circuitry underlying reward-related decisions and a set of functional hypotheses about why the circuitry is configured as it is. The state of our current knowledge remains well removed from that objective, and the model presented here has numerous limitations. In later sections, I discuss a strategy for moving forward.

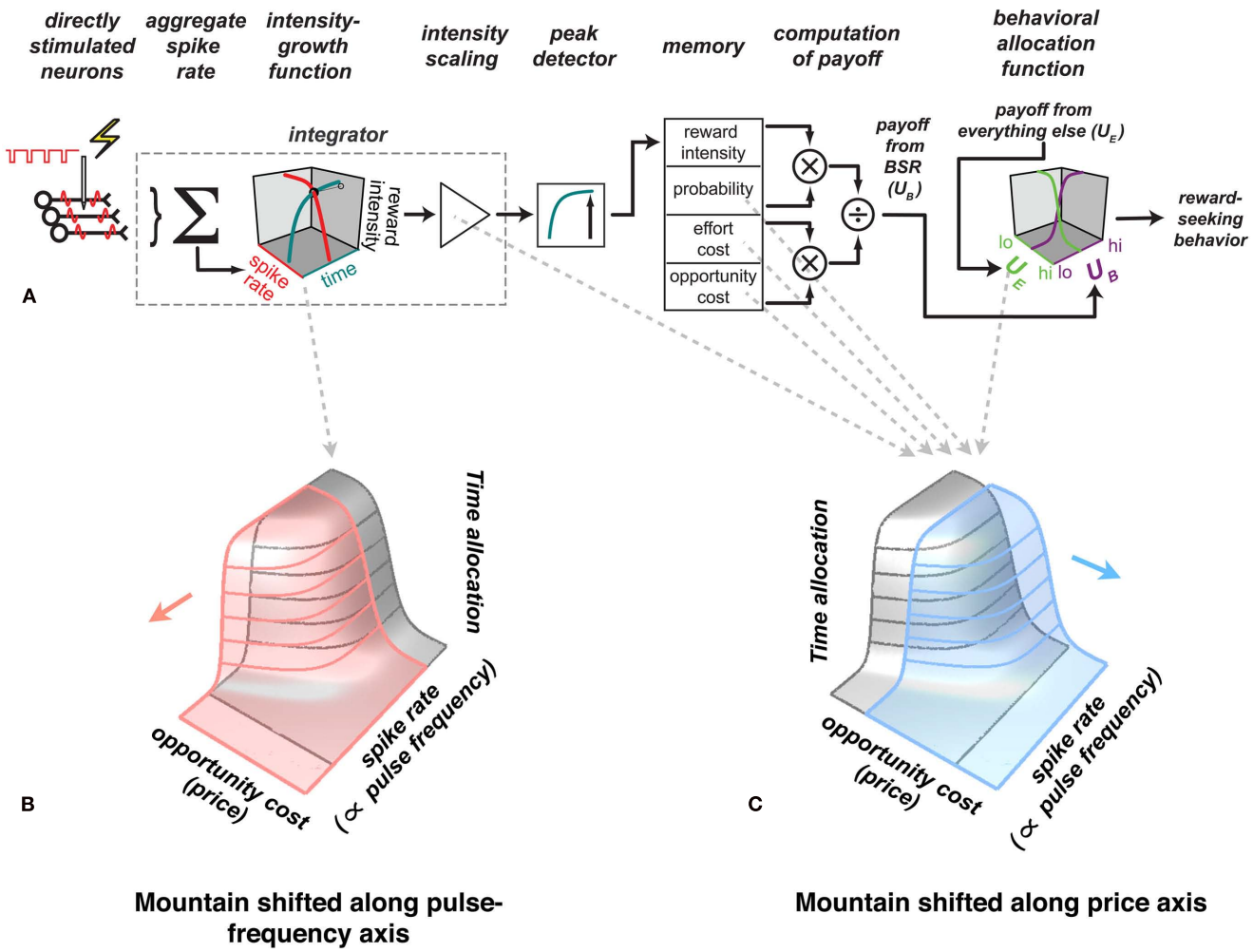

FIGURE 5 | Inferring the stages of processes responsible for shifts of the mountain. (A) The mountain model. Experimental manipulations that act on the early stages of processing, prior to the output of the intensity-growth function, shift the three-dimensional structure along the pulse frequency axis **(B)** whereas manipulations that act on later stages produce shifts along the price axis **(C)**. Thus, measuring the effects of such manipulations on the position of the three-dimensional structure constrains the stages of processing responsible for the behavioral effects of the manipulations. On this basis, the enhancement of reward seeking produced by cocaine (Hernandez et al., 2010) and the attenuation of reward seeking produced by blockade of cannabinoid CB-1 receptors (Trujillo-Pisanty et al., 2011) were shown to arise primarily from drug actions at stages of processing beyond the output of the intensity-growth function.

Let us consider various limitations as we traverse the schemata in **Figures 3** and **5** from right to left. The first one encountered is the behavioral-allocation function, which has been borrowed from the matching literature. This application is an "off-label" usage of an expression developed to describe matching of response rates on variable-interval schedules to reinforcement rates. As is the case with ratio schedules, returns from the cumulative handling-time schedule are directly proportional to investment (of time, in this case). The predicted behavior is maximization, not matching. The justification for our off-label usage is empirical: the observed behavior corresponds closely to the predicted form. That said, other sigmoidal functions would likely do the job. We have not yet explored alternative functions in this class and have chosen instead to investigate behavioral-allocation decisions on a finer time scale.

Data from operant conditioning studies are commonly presented in aggregate form, as response and reinforcement totals accumulated during some time interval (i.e., as trial rates). This is reminiscent of the way behavior is modeled in economic theories of consumer choice (Kagel et al., 1995). What matters in such accounts is not the order and timing with which different goods are placed in the shopping basket but rather the kinds of goods that make up the final purchase and their relative proportions. This is unsatisfying to the neuroeconomist. The goods enter the shopping basket as a result of some real-time decision making process. What is the nature of that process, and what is its physical basis? To answer such questions, a moment-to-moment version of the behavioral-allocation function must be developed. Only then can the behavioral data be linked directly to real-time measurements such as electrophysiological or neurochemical recordings. A successful solution would generate accurate predictions both at the scale of individual behavioral acts and at the scale of aggregate accumulations. Such a solution should be functionally plausible

in the sense that the behavioral strategies it generates not be dominated by alternatives available to competitors.

We have made an early attempt at real-time modeling (Conover et al., 2001) as well as at development of a behavioral-allocation model derived from first principles (Conover and Shizgal, 2005). Work on these initiatives is ongoing, but the formulation presented here appears adequate for its application in identifying circuitry underlying BSR, interpreting pharmacological data, and deriving psychophysical functions that contribute to reward-related decisions. For these purposes, we need the behavioral-allocation function to be only good enough to allow us to "see through it" (Gallistel et al., 1981) and draw inferences about earlier stages.

The computation of payoff is represented in **Figures 3** and **5** immediately upstream of the behavioral-allocation function. "Benefits" (reward intensity) are combined in scalar fashion with costs, as is the case in matching law formulations (Baum and Rachlin, 1969; Killeen, 1972; Miller, 1976). This way of combining benefits and costs contrasts sharply with "shopkeeper's logic," which dictates that both be translated into a common currency and their difference computed (e.g., Niv et al., 2007). The scalar combination posited in the mountain model is why sections obtained at different levels of reward intensity are parallel when plotted against a logarithmic price axis. We have observed such parallelism using a different schedule of reinforcement (Arvanitogiannis and Shizgal, 2008), but additional work should be carried out to confirm whether strict parallelism holds when the cumulative handling-time schedule is employed.

As we move leftward through the model, we reach the stages most directly under the control of the stimulating electrode. An important limitation of the model as it now stands is that even these stages are described only computationally – the neural circuitry underlying them has yet to be pinned down definitively, either in the case of electrically induced reward or of the rewarding effects of natural stimuli. Candidate pathways subserving BSR are discussed in the following section. The key point to make here is that this crucial limitation is one that the ICSS paradigm would seem particularly well suited to overcome. The powerfully rewarding effect of the electrical stimulation arises from a stream of action potentials triggered in an identifiable set of neurons. This should make the ICSS phenomenon an attractive entry point for efforts to map the structure of brain reward circuitry and to account for its functional properties in terms of neural signaling between its components. Section "Linking Computational and Neural Models" provides some reasons why success has not yet been achieved and why newly developed techniques promise to surmount the obstacles that have impeded progress. These new methods should make it possible to associate the abstract boxes in **Figures 3** and **5** with cells, spike trains and synaptic potentials in the underlying neural circuitry.

CANDIDATE NEURAL CIRCUITRY

In this section, I review some candidates for neural circuitry underlying BSR. This brief overview highlights some achievements of prior research as well as many challenges that have yet to be addressed in a satisfactory way.

The data in **Figures 1** and **2** were generated by stimulation delivered at the lateral hypothalamic (LH) level of the MFB. Kate Bielajew and I have provided evidence that the volley of action potentials elicited by stimulation at this site must propagate caudally in order the reach the efferent stages of the circuit responsible for the rewarding effect (Bielajew and Shizgal, 1986). **Figure 6** depicts some of the descending MFB components that course near the LH stimulation site as well as some of the circuitry connected to these neurons. Even this selective representation reveals a multiplicity of candidates for the directly stimulated neurons and spatio-temporal integrator in **Figures 3** and **5**.

Dopamine-containing neurons figure prominently in the literature on reward seeking in general (Wise and Rompré, 1989; Montague et al., 1996; Schultz et al., 1997; Ikemoto and Panksepp, 1999) and on BSR in particular (Wise and Rompré, 1989; Wise, 1996). Pursuit of BSR is attenuated by treatments that reduce dopaminergic neurotransmission (Fouriezos et al., 1978; Franklin, 1978; Gallistel and Karras, 1984) and is boosted by treatments that enhance such signaling (Crow, 1970; Gallistel and Karras, 1984; Colle and Wise, 1988; Bauco and Wise, 1997; Hernandez et al., 2010). Both long-lasting ("tonic") and transient ("phasic") release of dopamine are driven by rewarding MFB stimulation (Hernandez and Hoebel, 1988; You et al., 2001; Wightman and Robinson, 2002; Hernandez et al., 2006, 2007; Cheer et al., 2007). **Figure 6** shows that the axons of midbrain dopamine neurons course through the MFB, passing close to the LH stimulation sites used in many studies of ICSS (Ungerstedt, 1971). Direct activation of dopaminergic fibers by rewarding stimulation was central to early accounts of ICSS (German and Bowden, 1974; Wise, 1978; Corbett and Wise, 1980). Nonetheless, these authors did express some reservations, which turn out to be well founded. The axons of dopamine neurons are fine, unmyelinated, and difficult to excite by means of extracellular stimulation (Yeomans et al., 1988; Anderson et al., 1996; Chuhma and Rayport, 2005). The mere proximity of these axons to the electrode tip does not guarantee that a large proportion of them are excited directly under the conditions of ICSS experiments. Indeed, the electrophysiological properties of these fibers provide a poor match to the properties inferred from behavioral studies of ICSS (Yeomans, 1975, 1979; Bielajew and Shizgal, 1982, 1986). These behavioral data suggest that non-dopaminergic neurons with descending, myelinated axons, more excitable than those of the dopamine-containing cells, compose an important part of the directly stimulated stage (Bielajew and Shizgal, 1986; Shizgal, 1997). Non-dopaminergic neurons driven by rewarding MFB stimulation, and with properties consistent with those inferred from the behavioral data, have indeed been observed by electrophysiological means (Rompré and Shizgal, 1986; Shizgal et al., 1989; Kiss and Shizgal, 1990; Murray and Shizgal, 1996).

Figure 6 provides several different ways to reconcile the dependence of ICSS on dopaminergic neurotransmission with the evidence implicating non-dopaminergic neurons in the directly stimulated stage of the circuit. Multiple components of the descending MFB provide monosynaptic input to dopamine cell bodies in the midbrain, and glutamatergic neurons are prominent among them (You et al., 2001; Geisler et al., 2007). Blockade of glutamatergic receptors on midbrain dopamine neurons decreases transient release of dopamine by rewarding electrical stimulation (Sombers et al., 2009). Cholinergic neurons in the pons constitute one limb of a disynaptic path that links MFB electrodes to activation of

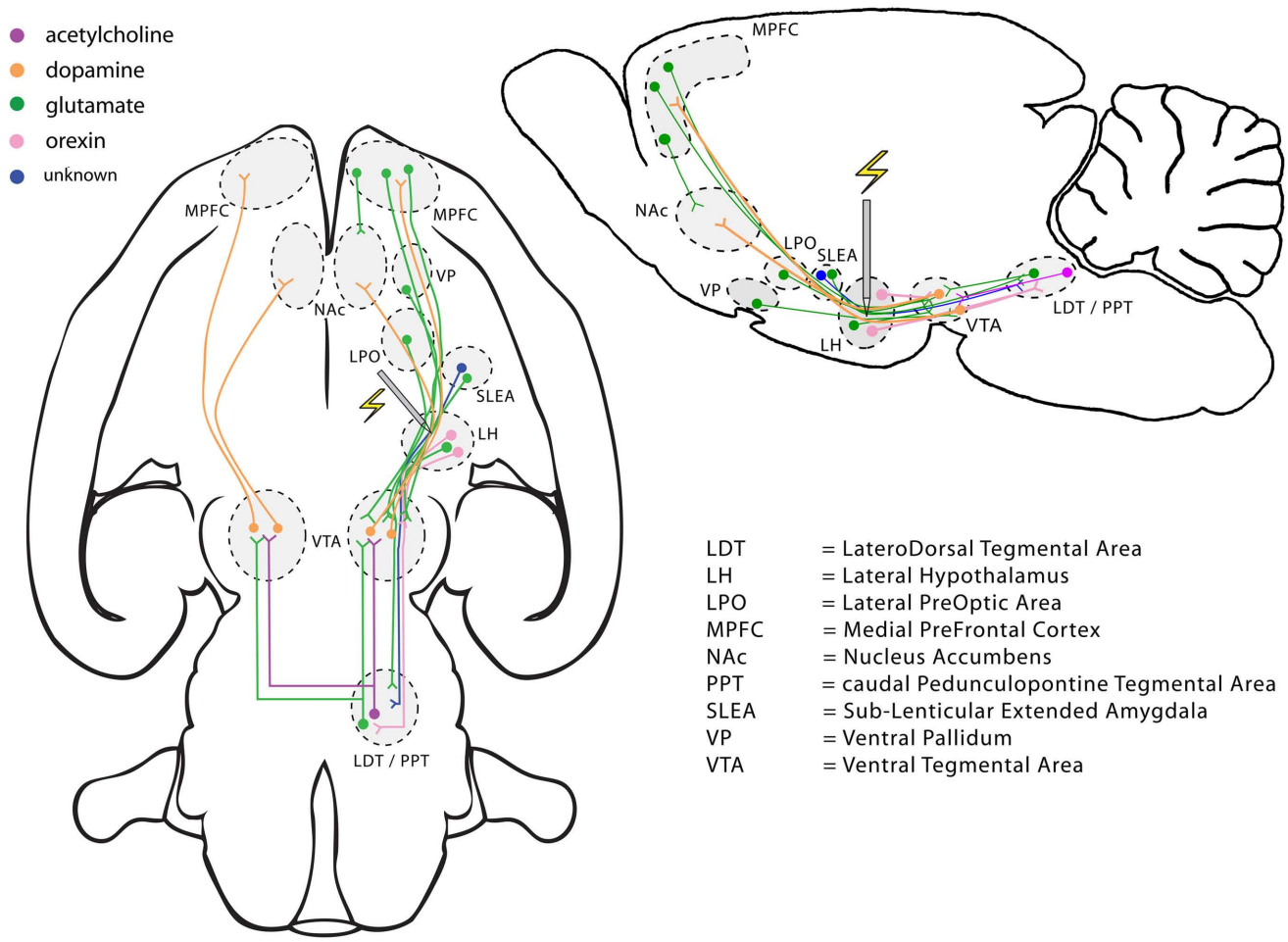

FIGURE 6 | Selected descending pathways coursing through a lateral hypothalamic region of the medial forebrain bundle, where electrical stimulation is powerfully rewarding, and some associated neural circuitry. The lefthand view is in the horizontal plane and the righthand view in the sagittal plane.

dopamine neurons (Oakman et al., 1995). These cholinergic neurons are implicated in the rewarding effect of MFB stimulation (Yeomans et al., 1993, 2000; Fletcher et al., 1995; Rada et al., 2000).

It has been proposed, in the case of posterior mesencephalic stimulation, that the spatio-temporal integration of the reward intensity signal arises prior to, or with the participation of, midbrain dopamine neurons (Moisan and Rompre, 1998). Application of this idea to self-stimulation of the MFB is consistent with the evidence that excitation driven by the rewarding stimulation arrives at the dopamine neurons via monosynaptic and/or disynaptic routes. Given the important roles ascribed to dopaminergic neurons in the allocation of effort and in reward-related learning, it is important to understand how information is processed in their afferent network. By driving inputs to the dopaminergic neurons directly, rewarding brain stimulation should play a useful role in this endeavor and should continue to contribute to the ongoing debate about the functional roles of phasic and tonic dopamine signaling (Wise and Rompré, 1989; Salamone et al., 1997, 2005; Schultz et al., 1997; Berridge and Robinson, 1998; Schultz, 2000; Wise, 2004; Niv et al., 2007; Berridge et al., 2009).

The preceding paragraphs attest to the fact that it has proved simple neither to identify the neurons composing the most accessible stage of the circuitry underlying ICSS, the directly activated stage, nor to determine the precise role played by the neural population most extensively studied in the context of BSR, midbrain dopamine neurons. In the following section, I discuss in more general terms the requirements for establishing such linkages, and I argue that new research techniques provide grounds for optimism that long-standing obstacles can be overcome.

LINKING COMPUTATIONAL AND NEURAL MODELS

Multiple, converging, experimental approaches are required to link an identified neural population to a psychological process (Conover and Shizgal, 2005). Each approach tests the linkage hypothesis in a different way, by assessing correlation, necessity, modulation, sufficiency or computational adequacy. All of these approaches have been applied in the search for the directly stimulated neurons underlying BSR and in efforts to determine the role played by midbrain dopamine neurons. Nonetheless, the full promise of the convergent strategy has yet to be realized.

An example of a correlational test has already been mentioned. Inferences are drawn from behavioral data about physiological properties of a neural population, such as the directly stimulated neurons that give rise to BSR. A method such as single-unit electrophysiology is used to measure neural properties, which are then compared to those inferred from the behavioral data. For example, the experimenter can ascertain, by means of collision between spontaneous and electrically triggered antidromic spikes, that the axon of a neuron from which action potentials are recorded is directly activated by rewarding stimulation. Properties of the stimulated axon, such as its refractory period and conduction velocity, are then measured and compared to those inferred from the behavioral data (Shizgal et al., 1989; Murray and Shizgal, 1996). This approach can provide supporting evidence for a linkage hypothesis, but it cannot prove it. The portrait assembled on the basis of the behavioral data is unlikely to be unique, and the neuron under electrophysiological observation may resemble those responsible for the behavior in question but, in fact, subserve another function.

Tests of necessity entail silencing the activity of some population of neurons and then measuring any consequent changes in the behavior under study. Traditional methods include lesions, cooling, and injection of local anesthetics. Although this approach can also provide supporting evidence, it is fraught with difficulties. Many neurons in addition to the intended targets may be affected, and the silencing may alter the behavior under study in unintended ways, for example, by reducing the capacity of the subject to perform the behavioral task rather than the subjective value of the goal. The typically employed silencing methods have durations of action far longer than those of the neural signals of interest.

Tests of modulation are similar logically to tests of necessity but can entail either enhancement or suppression of neural signaling and are usually reversible. Drug administration is typically employed for this purpose. This approach often achieves greater specificity than is afforded by conventional silencing methods. Nonetheless, it is difficult to control the distribution of a drug injected locally in the brain, and the duration of drug action often exceeds that of the neural signal of interest by many orders of magnitude.

Tests of sufficiency entail exogenous activation of a neural population and determination of whether the artificially induced signal so produced affects the psychological process under study in the same way as a natural stimulus. The demonstration that the rewarding effect of electrical stimulation of the MFB competes and summates with the rewarding effect of gustatory stimuli (Conover and Shizgal, 1994; Conover et al., 1994) is an example of this approach. Traditional sufficiency tests, which often entail delivery of electrical brain stimulation, provide much better temporal control than local drug injection, but they too are plagued by major shortcomings: Many neurons in addition to the target population are typically activated, and the stimulation may produce undesirable behavioral side-effects.

Computational adequacy is another important criterion for establishing linkage. To carry out this test, a formal model is built, such as the one in **Figures 3** and **5**, and the role of the neural population under study is specified. Simulations are then performed to determine whether the model can reproduce the behavioral data using the parameters derived from neural measurement. This is a demanding test, but it too is not decisive. There is no guarantee that any given model is unique or sufficiently inclusive.

Although all its elements have shortcomings as well as virtues, the convergent strategy is nonetheless quite powerful. The virtues of some elements compensate for the shortcomings of others, and the likelihood of a false linkage decreases as more independent and complementary lines of evidence are brought to bear. That said, one may well wonder why, if the convergent approach is so powerful, has it not yet generated clear answers to straightforward questions such as the identity of the directly stimulated neurons subserving BSR or the role played by midbrain dopamine neurons? As I argue in the following section, many of the problems are technical in nature, and recent developments suggest that they are in the process of being surmounted.

THE PROMISE OF NEW RESEARCH TECHNIQUES

Ensemble recording

The example of the correlational approach described above entails recording from individual neurons, one at a time, in anesthetized subjects, after the collection of the behavioral data. Newer recording methods have now been developed that register the activity of dozens of neurons simultaneously while the behavior of interest is being performed. A lovely example of this substantial advance is a recent study carried out by a team led by David Redish (van der Meer et al., 2010). They recorded from ensembles of hippocampal neurons as rats learned to navigate a maze. As the rats paused at a choice point during a relatively early stage of learning, these neurons fired in patterns similar to those recorded previously as the animal was actually traversing the different paths. This demonstration supports Tolman's (1948) idea that animals can plan by means of virtual navigation in stored maps of their environment. Tolman's theory was criticized for leaving the rat "lost in thought." The study by van der Meer et al. (2010) suggests that the rat is not lost at all but is instead exploring its stored spatial representation. This is a powerful demonstration of the potential of neuroscientific methods to open hidden states to direct observation.

The correlational approach adopted by van der Meer et al. (2010) was complemented by a test of computational adequacy: they determined the accuracy with which the population of neurons from which they recorded could represent position within the maze. Another aspect of their study dissociated the correlates of hippocampal activity from those of neurons in the ventral striatum, one of the terminal fields of the midbrain dopamine neurons. Unlike the activity of the hippocampal population, the activity of the ventral–striatal population accelerated as the rats approached locations where they had previously encountered rewards (van der Meer and Redish, 2009; van der Meer et al., 2010). This ramping activity was also seen at choice points leading to the locations in question. The authors point out that such a pattern of anticipatory firing, in conjunction with the predictive spatial information derived from hippocampal activity, could provide feedback to guide vicarious trial-and-error learning.

Once the neurons underlying BSR have been identified, it would be very interesting indeed to study them by means of

ensemble recording methods. Such an approach could provide invaluable information about the function of the BSR substrate and might well explain how reward-related information is relayed to ventral–striatal neurons. In principle, ensemble recording from the appropriate neural populations could provide physical measurement of the subjective values of economic variables in real-time. This could go a long way toward putting to rest criticisms of models that incorporate states hidden to the outside observer, such as the one detailed in **Figures 3** and **5**. Ensemble recording coupled to appropriate computational methods promises to draw back the veil.

Chronic, in vivo voltammetry

Just as ensemble recording registers the activity of neural populations during behavior, *in vivo* voltammetry (Wightman and Robinson, 2002) can measure dopamine transients during performance of economic decision making tasks. In early studies, the measurements were obtained acutely over periods of an hour or so. However, Phillips and colleagues have now developed an electrode that can register dopamine transients over weeks and months (Clark et al., 2010), periods sufficiently long for the learning and execution of demanding behavioral tasks. Their method has already yielded dramatic results in neuroeconomic studies (Gan et al., 2010; Wanat et al., 2010; Nasrallah et al., 2011), and its application would provide a strong test of the hypothesis that phasic activity of midbrain dopamine neurons encodes the integrated reward intensity signal in ICSS.

Optogenetics

The recent development with the broadest likely impact is a family of "optogenetic" methods (Deisseroth, 2011; Yizhar et al., 2011). These circumvent the principal drawbacks of traditional silencing and stimulation techniques, achieving far greater temporal, spatial, and cell-type selectivity, while retaining all the principal advantages of the traditional tests for necessity and sufficiency. This technology is based on light-sensitive, microbial opsin proteins genetically targeted to restricted neuronal populations. Following expression, the introduced opsins are trafficked to the cell membrane, where they function as ion channels or pumps. By means of fiber-optic probes, which can be implanted and used chronically in behaving subjects, light is delivered to a circumscribed brain area, at a wavelength that activates the introduced opsin. Neural activity is thus silenced or induced for periods as short as milliseconds or as long as minutes.

The means for specific activation and silencing of dopaminergic (Tsai et al., 2009), cholinergic (Witten et al., 2010), glutamatergic (Zhao et al., 2011), and orexinergic (Adamantidis et al., 2007) neurons have already been demonstrated. Coupled with measurement methods such as the one that generated the data in **Figures 1** and **2**, application of optogenetic tools should reveal what role, if any, the different elements depicted in **Figure 6** play in BSR. Indeed, it has already been shown by specific optogenetic means that activation of midbrain dopamine neurons is sufficient to support operant responding (Kim et al., 2010; Adamantidis et al., 2011; Witten et al., 2011). However, it remains unclear whether such activation fully recapitulates the rewarding effect of electrical stimulation or only a component thereof; the stage of processing at which the dopaminergic neurons intervene has not yet been established.

FROM BRAIN STIMULATION REWARD TO NATURAL REWARDS

Many decades have passed since BSR was discovered (Olds and Milner, 1954), but the neural circuitry underlying this striking phenomenon has yet to be worked out. Ensemble recordings, chronic *in vivo* voltammetry, and optogenetics promise to produce revolutionary change in the way this problem is approached and to circumvent critical technical obstacles that have blocked or impeded progress. Once components of the neural substrate for BSR have been identified, the convergent approaches described above can be brought to bear, with greatly increased precision and power, in the growing array of tasks for studying economic decision making in non-human animals. This will provide a natural bridge between the specialized study of BSR and the more general study of neural mechanisms of valuation and choice.

Kent Conover and I have developed a preparation (Conover and Shizgal, 1994) in which gustatory reward can be controlled with a precision similar to that afforded by BSR. The gustatory stimulus is introduced directly into the mouth, and a gastric cannula undercuts the development of satiety. Psychophysical data about the gustatory reward can be acquired from this preparation at rates approaching those typical of BSR studies. This method should make it possible to carry out a test, at the neural level, of the hypothesis that BSR and gustatory rewards are evaluated in a common currency. It can also render some fundamental questions about gustatory reward amenable to mechanistic investigation. For example, it has long been suspected that the thalamic projection of the pontine parabrachial area mediates discriminative aspects of gustation whereas the basal forebrain projections mediate the rewarding effects of gustatory stimuli (Pfaffmann et al., 1977; Spector and Travers, 2005; Norgren et al., 2006). Application of methodology developed for the study of BSR can put this notion to a strong test. Other basic questions that beg to be addressed concern the dependence of gustatory reward on energy stores. Within the framework of the model described in **Figures 3** and **5**, how do deprivation states act? Do they modulate early stages of processing, thus altering preference between different concentrations of a tastant of a particular type and/or do they act at later stages so as to alter preference between different classes of tastants, such as inputs to short- and long-term energy stores (Hernandez et al., 2010)?

Questions such as those posed in the preceding paragraph concern basic topics that economists have long abstained from addressing: the origin of preferences, their dependence on internal conditions, and the possibility that an important aspect of individual differences in valuation derives from constitutional factors. In Robbins' account, the agent arrives on the economic stage already equipped with a set of "tastes" (i.e., preferences in general and not only gustatory ones). What is the physical basis of these tastes? What mechanisms change them? What determines when tastes serve biologically adaptive purposes or lead in harmful directions? Developments in the neurosciences may have rendered such questions addressable scientifically and may even be up to the challenge of providing some answers.

A QUADRUPLE HERESY

I begin this essay within the canon of Robbins' greatly influential definition of economics and then proceed to commit four heresies. First, I extend Robbins' core concept of allocation under scarcity to non-human animals. Second, I make common cause with behavioral economists, who strive to base their theories of the economic agent on realistic psychological foundations, and I argue that psychophysics constitutes one of the fundamental building blocks of this structure. Third, I argue that sentience is not necessary for economic behavior. Fourth, I advocate grounding the theory of the economic agent in neuroscience, to the extent that our knowledge and methods allow. I predict that this initiative should lead to new insights, render otherwise hidden states amenable to direct observation, and provide a way to choose between models that appear equally successful when evaluated on the behavioral and computational levels alone.

Economic concepts have long played a central role in behavioral ecological studies of non-human animals (Stephens and Krebs, 1986; Commons et al., 1987; Stephens et al., 2007). It seems to me highly likely that machinery enabling other animals to make economic decisions has been conserved in humans and very unlikely indeed that this inheritance lies defunct and unused as we strive to navigate the choices confronting us.

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Discounting in pigeons when the choice is between two delayed rewards: implications for species comparisons

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Studies of delay discounting typically have involved choices between smaller, immediate outcomes and larger, delayed outcomes. In a study of delay discounting in humans, Green et al. (2005) added a period of time prior to both outcomes, creating a delay common to both. They found that the subjective value of the more delayed reward was well described by a hyperboloid discounting function and that the degree to which that outcome was discounted decreased as the common delay increased. In two experiments, we examined the effect of adding a common delay on the discounting of food rewards in pigeons. In Experiment 1, an adjusting-amount procedure was used to establish discounting functions when the common delay was 0, 3, 5, and 10 s, and different stimuli signaled time to the smaller, sooner and larger, later rewards. In contrast to humans, the pigeons showed increases in the degree of discounting when a common delay was added. In Experiment 2, the delay common to both rewards and the delay unique to the larger, later reward were each specifically signaled. With this procedure, the degree of discounting decreased as the common delay increased, a result consistent with that obtained with humans (Green et al., 2005). These findings reveal fundamental similarities between pigeons' and humans' choice behavior, and provide strong interspecies support for the hypothesis that choice between delayed outcomes is based on comparison of their hyperbolically discounted present subjective values.

Keywords: delay discounting, hyperbolic, discounting function, pigeons, humans

INTRODUCTION

People and other animals often have to choose between an immediate reward and another, larger reward of the same kind that is available only after a delay. When the delay to the later reward is long, a small amount of immediate reward may be chosen over the delayed reward, but if the delay is brief, then the choice may be to wait for the larger reward. This difference in preference is assumed to reflect the fact that the value of a delayed reward is discounted, with longer delays leading to greater discounting, and it is observed in both humans (Green et al., 1994; Kirby, 1997) and non-human species (rat and pigeon, Richards et al., 1997; Mazur, 2000; Green et al., 2004; monkey, Freeman et al., 2009). The decrease in the value of a reward as the delay to its receipt increases is well described by a simple hyperbolic function (Mazur, 1987):

$$V = A/(1+kD), \tag{1}$$

where V is the subjective value of the delayed reward, A is the amount of the delayed reward, and D is its delay. The parameter k governs the degree of discounting, with larger values indicating steeper discounting[1].

Often, of course, the choice is not between an immediate and a delayed reward, but rather between two delayed rewards. If the sooner reward is also the larger one, choice is straightforward, but when the sooner reward is smaller, then the decision is more complicated. For example, consider the situation depicted in **Figure 1**, in which the heights of the bars represent the actual (undiscounted) value of two rewards and the curved lines depict their subjective (i.e., discounted) values as predicted by Eq. 1. The likelihood of choosing a particular alternative at any point in time depends on the relative subjective values of the two rewards. As may be seen, choice of the larger reward is more likely if the decision is made at an earlier point in time (e.g., at T_1), whereas choice of the smaller reward is more likely if the decision is made later (e.g., at T_2). Indeed, both humans and non-human animals show the preference reversals predicted by **Figure 1** (e.g., Ainslie and Herrnstein, 1981; Green et al., 1981, 1994).

The present study provides a systematic examination of choice between delayed rewards in pigeons and a test of the mechanism that is hypothesized to underlie such choices. In two experiments, the delays to the smaller, sooner and larger, later rewards were varied, as was the amount of the smaller, sooner reward, while the amount of the larger, later reward was held constant. The amount of time corresponding to the delay from the choice point until the smaller, sooner reward (designated A in **Figure 1**) is common to both alternatives, whereas the delay from the choice point to the larger, later reward consists of the common delay plus an additional delay (designated B in **Figure 1**) that is unique to the larger, later reward.

The framework depicted in **Figure 1**, which implicitly assumes that choices are made based on comparison of the present subjective values of hyperbolically discounted outcomes, predicts that the

[1]Typically, human delay discounting data are better described by a generalized form of Eq. 1 in which the denominator is raised to a power (e.g., Myerson and Green, 1995), but a simple hyperbola (i.e., the special case where the exponent equals 1.0) usually suffices to describe data from non-human animals.

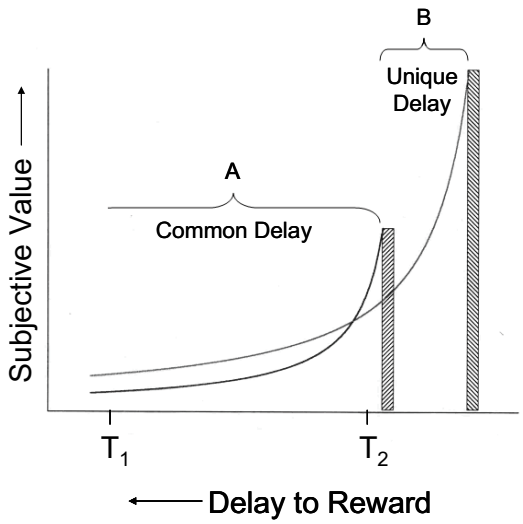

FIGURE 1 | Hyperboloid discounting of smaller, sooner and larger, later rewards. The *x*-axis represents the time until a reward, and the *y*-axis represents its subjective value. The portion of the delay that is common to both the smaller, sooner and larger, later rewards is labeled A, and the portion of the delay to the larger, later reward that is unique is labeled B.

subjective value of the larger, later reward should be discounted less steeply when the common period is longer, and indeed, this result was observed in humans by Green et al. (2005). To see why this is so, consider that according to Eq. 1, the subjective value of the smaller, sooner reward (V_S) is given by

$$V_S = A_S/(1+kD_c) \tag{2a}$$

and the subjective value of the larger, later reward (V_L) is given by

$$V_L = A_L/[1+k(D_c+D_u)], \tag{2b}$$

where A_S and A_L are the amounts of the sooner and later rewards, respectively, D_c and D_u are the common and unique portions of the delay to the later reward (see **Figure 1**).

It follows from the preceding two equations that the amount of the sooner reward that will be equal in subjective value to the later reward is given by

$$A_S = A_L/(1+kD_c)/[1+k(D_c+D_u)]$$

Expanding the denominator, dividing both the numerator and denominator by $(1 + k\,D_c)$, and rearranging yields

$$A_S = A_L/\{1+[k/(1+kD_c)]D_u\},$$

which may be rewritten as

$$A_S = A_L/(1+k'D_u), \tag{3}$$

where $k' = k/(1 + k\,D_c)$. It may be seen that as the duration of the common delay, D_c, increases, the value of the fraction $k/(1 + k\,D_c)$ decreases. Thus, Eq. 1 predicts that when the choice is between a smaller, sooner reward and a larger, later reward, discounting will be hyperboloid in form, and as the common delay increases, the parameter k' will decrease, leading to shallower discounting. Note that whereas k governs the degree of discounting when subjective value is measured in terms of the amount of immediate reward, k' governs the rate of discounting when subjective value is measured in terms of the amount of delayed reward (available at the end of the common delay).

Because the same equation (Eq. 1) fits delay discounting data from both humans and pigeons when choice is between an immediate and a delayed reward, the question arises as to whether the extension of this equation to choice between two delayed rewards (represented by Eqs 2a, 2b, and 3) describes pigeon as well as human data. In two experiments, pigeons chose between smaller amounts of food available after a shorter delay and larger amounts of food available after a longer delay. An adjusting-amount procedure was used to estimate the amount of the smaller, sooner reward that was approximately equal in subjective value to the larger, later reward. The two experiments differed in how the common and the unique portions of the delays were signaled. In Experiment 1, pigeons' choices between delayed rewards appeared to be quite different from humans, suggesting that quite different decision processes were involved. In Experiment 2, however, when signals were provided to facilitate discrimination of the common and unique portions of the delay to the later reward, the pigeons' choices were similar to those of humans in analogous situations.

EXPERIMENT 1

METHOD

Subjects

Five naïve, female White Carneau pigeons (numbered P15–P19) were individually housed in an animal colony room with a 12:12-h light/dark cycle. The pigeons had water and health grit continuously available in their home cages, and they were provided supplemental post-session food (Pigeon Checkers) to maintain their weights between 80 and 85% of their individually determined free-feeding body weights. The experiments were performed in accordance with relevant institutional and national guidelines and regulations, and were approved by the Animal Studies Committee of Washington University.

Apparatus

Two experimental chambers (Coulbourn Instruments, Inc.) were used, each measuring 28 cm long, 23 cm wide, and 30.5 cm high. The experimental chambers were enclosed within sound- and light-attenuating chambers equipped with ventilation fans that also provided masking noise during experimental sessions. A MED Associates interface and MED-PC™ software running on a personal computer located in an adjacent room were used to present stimuli and record responses.

Three response keys, spaced 8 cm apart, were mounted on the front panel of each experimental chamber. The right- and left-most keys (which could be transilluminated green and red, respectively) were 25 cm above the grid floor and 3.5 cm from the side walls of the chamber. The center response key (which could be transilluminated yellow) was 21 cm above the grid floor and mounted in the center of the front panel. A triple-cue light was mounted 6 cm above the center key, and could be illuminated red, yellow, and green (from left to right). A 7-W house light, mounted on the ceiling

of the chamber, provided ambient illumination. A food magazine was located below the right key and another magazine was located below the left key; in both cases, the bottom of the magazine was 4 cm above the grid floor. Food pellets (20-mg pellets; TestDiet, Formula 5TUZ) were dispensed at a rate of one every 0.3 s. There was a 7-W light located inside each magazine to provide illumination during reinforcement and an infrared photo-detector to detect when a pigeon's head entered and left the magazine.

Procedure

Pigeons were trained to peck the response keys, following which they were studied daily using a discrete-trials procedure in which each block of trials consisted of two forced-choice trials followed by two free-choice trials. Of the two forced-choice trials, one was a smaller–sooner-reward trial and the other was a larger–later-reward trial; which type of trial was first was varied randomly across blocks. Experimental sessions were conducted daily and ended either after 40 blocks of trials or after 75 min had elapsed, whichever came first.

The beginning of all trials, both free- and forced-choice, was signaled by the illumination of the center yellow response key and the yellow cue light. On free-choice trials, a single response darkened both the center key and the yellow cue light and illuminated the right (green) and left (red) side keys as well as the green and red cue lights. The red side key was associated with a larger, later reward (30 food pellets), and the green side key was associated with a smaller, sooner reward (an adjusting number of pellets). A single response on either side key darkened both side keys. If the left key was pecked, the green cue light was extinguished and the red cue light remained illuminated; if the right key was pecked, the red cue light was extinguished and the green cue light remained illuminated. On forced-choice trials, only one side key and its associated cue light were illuminated; a single response darkened the key but not the cue light.

Pigeons experienced a delay to reinforcement on every trial. As depicted in **Figure 1**, the time until the smaller, sooner reward was the common delay (corresponding to A in the figure), and the time until the larger, later reward consisted of two intervals: the common delay plus a unique delay specific to the later reward (corresponding to B in the figure). On smaller–sooner-reward trials, the green cue light and the house light remained illuminated until the common delay elapsed, at which point the right magazine light was illuminated and an adjusting number of pellets was delivered. On larger–later-reward trials, the red cue light and the house light remained illuminated through the common delay and until the unique delay elapsed, at which point the left magazine light was illuminated and 30 pellets were delivered. The magazine light remained illuminated until 3 s had elapsed since the pigeon removed its head from the magazine, after which the magazine light was extinguished and the house light was illuminated. A new trial began 70 s after the pigeon had made its choice (i.e., pecked a side key) on the preceding trial.

The (common) delay to the smaller, sooner reward was either 0, 3, 5, or 10 s, depending on the condition (plus an additional 0.5 s to allow the pigeon time to get its head down to the magazine; Mazur, 2000). Within each common-delay condition, there were four unique-delay conditions (2, 5, 10, and 25 s). For example, in the 25-s unique-delay condition of the 3-s common-delay condition, the pigeon chose between an adjusting number of pellets that could be received after 25 s and 30 pellets that could be received after 28 s (again, plus an additional 0.5 s). For each pigeon, a unique-delay condition was terminated once the subjective value of the larger, later reward was determined. Once all the unique-delay conditions within a common-delay condition had been completed, a new common-delay condition began. The order of common-delay conditions and the order of unique-delay conditions at each common delay (16 conditions in all) were varied non-systematically across pigeons.

In the first block of the first session of each condition, the amount of the smaller, sooner reward was one pellet. Within each session, the amount of the smaller, sooner reward was adjusted from one block of trials to the next in order to determine the amount of smaller, sooner reward that subjects judged equal in value to the larger (30-pellet), later reward. If a pigeon chose the smaller, sooner reward on both free-choice trials in a block, then the amount of smaller, sooner reward was decreased by one pellet for the next block of trials; if the pigeon chose the larger, later alternative on both free-choice trials in a block, then the amount of the smaller, sooner reward was increased by one pellet for the next block of trials. Otherwise, the amount of the smaller, sooner reward remained the same for the next block of trials. The amount of sooner reward in the last block of trials of a session was used as the initial amount of smaller, sooner reward in the following session of the current condition.

Conditions were run for a minimum of 200 blocks and ended when a pigeon's preference was judged stable, indicating that the smaller, sooner reward was equal in value to the larger, later reward. To assess stability, the last 50 blocks of trials were divided into 10 groups of five consecutive blocks each, and both the overall mean amount of smaller, sooner reward for the 50 blocks of trials and the mean for each of the ten five-block groups were determined. Preference was considered to be stable when (i) none of the means of the 10 groups deviated by more than two pellets from the overall mean, (ii) neither the first nor the last of these 10 group means contained the highest or the lowest amount, and (iii) there was no upward or downward trend in the group means.

Results and Discussion

Figure 2 shows the amount of smaller, sooner reward equal in value to the later 30-pellet reward (i.e., the subjective value of the later reward measured in pellets available at the end of the common delay) plotted as a function of the unique delay. The curved lines represent Eq. 1 with D equal to the duration of the unique delay. **Table 1** shows the estimated k parameters (higher values indicate steeper discounting) and R^2s for each pigeon. In the 0-s common-delay condition, in which pigeons were choosing between an almost immediate reward and a larger, later reward, discounting was comparable to that observed in previous discounting studies with pigeons (e.g., Mazur, 2000; Green et al., 2004). When the common delay was increased, however, pigeons discounted the value of the larger, later reward much more steeply. This finding is clearly inconsistent with the predictions of Eq. 3 and opposite to what has been observed when human subjects discount delayed hypothetical monetary rewards (Green et al., 2005); for humans, the degree of discounting *decreased* as the common delay increases.

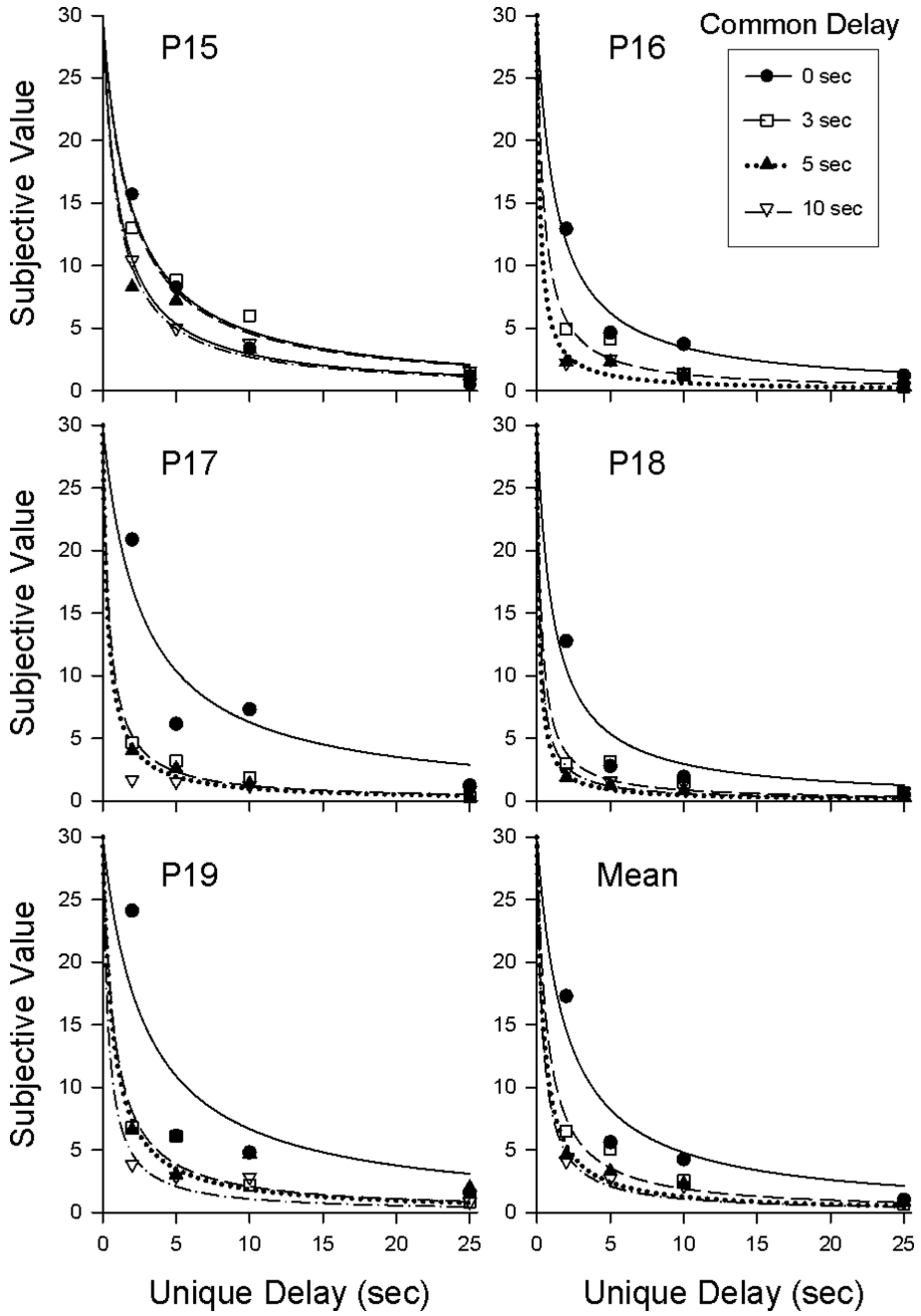

FIGURE 2 | Discounting of the larger, later reward in the 0-, 3-, 5-, and 10-s common-delay conditions in Experiment 1. Symbols represent subjective values (in pellets) for the four common-delay conditions. Curves represent the best-fitting discounting functions (Eq. 1).

Caution is required, of course, before concluding that this difference in results between pigeons and humans represents a true species difference in decision making. For one thing, different procedures typically are used when studying different species. In the present case, the pigeons received real, biologically important reinforcers, and experienced the delays associated with their delivery on every trial, whereas in the Green et al. (2005) study, the participants neither received the reward nor experienced the delay, but rather were asked to imagine the choices they would make if the delays and rewards were real. It is unclear, however, how these differences could lead to opposite findings like the difference between the present results and those of Green et al. (2005).

Another notable difference between the human and pigeon procedures may be in the salience of the common delay. In one condition of the Green et al. (2005) study, for example, participants were asked to choose between a smaller amount of money available in 2 years and a larger amount available in 2 years and 6 months. Thus, the durations of both the common delay (2 years) and the

Table 1 | The estimated *k* parameter and the proportion of variance in subjective values accounted for by Eq. 1 for each individual pigeon in each common-delay (CD) condition of Experiment 1.

	Common delay							
	0″ CD		3″ CD		5″ CD		10″ CD	
Subject	*k*	R^2	*k*	R^2	*k*	R^2	*k*	R^2
P15	0.53	0.96	0.55	0.93	1.01	0.75	0.92	0.98
P16	0.76	0.95	2.14	0.79	4.60	0.28	4.48	0.00
P17	0.38	0.83	2.38	0.85	2.91	0.91	6.38	0.00
P18	0.92	0.86	3.40	0.21	6.56	0.72	4.95	0.10
P19	0.35	0.77	1.36	0.74	1.53	0.16	2.69	0.03

Values of the k parameter were estimated by fitting Eq. 1, with D equal to the duration of the unique delay, to the data from each delay condition.

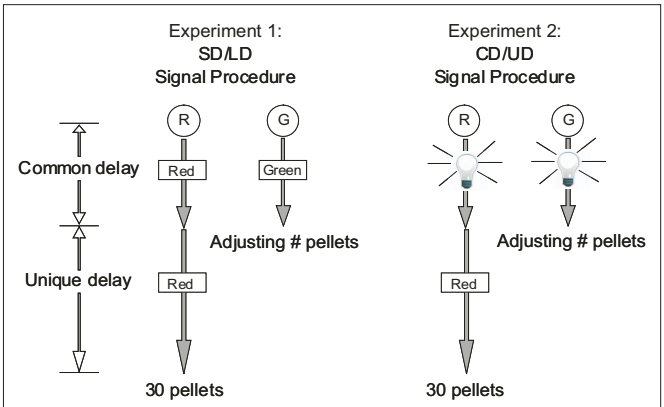

FIGURE 3 | Procedures for Experiments 1 and 2. SD and LD refer to the shorter and longer delays to reinforcement; CD refers to the portion of the delay to the smaller, sooner and larger, later rewards that they have in common, and UD refers to the portion of the delay to the larger, later reward that is unique to that reward. The circles at the top represent the response keys (R = red; G = green), the rectangles represent the cue lights, and the light bulbs represent the flashing house light.

unique delay (6 months) were specifically indicated. Even in a condition where the choice was between a smaller amount available in 2 years and a larger amount available in 7 years, participants could easily reframe the choice in terms of a common delay of 2 years and a unique delay of 5 years. In contrast, pigeons chose between a smaller reward available after a brief delay, signaled by one stimulus (a green cue light), and a larger reward available after a longer delay, signaled by a different stimulus (a red cue light), and there was nothing to specifically signal the portion of time common to both delayed rewards.

It seemed possible that a difference in the salience of the common and unique delays between the human and pigeon experiments was responsible for the difference in the results. In Experiment 2, therefore, we changed the stimuli to more clearly signal the common and unique delays. Specifically, the same stimulus that was present during the (common) delay until the smaller, sooner reward was also present during the initial (common) portion of the delay until the larger, later reward; on trials ending in a larger, later reward, a different stimulus signaled the final (unique) portion of the delay. Whereas in Experiment 1, different stimuli signaled the shorter delay and the longer delay (SD/LD-signal procedure), in Experiment 2, different stimuli signaled the common delay and the unique delay (CD/UD-signal procedure). Other aspects of the procedure, as well as the subjects, remained unchanged from Experiment 1.

EXPERIMENT 2

METHOD

Subjects and apparatus

The subjects and apparatus were the same as in Experiment 1.

Procedure

The procedure was basically the same as in Experiment 1 with the principal exception being the way in which the common and unique delays were signaled (compare the SD/LD-signal procedure used in Experiment 1 with the CD/UD-signal procedure used in Experiment 2, as shown in **Figure 3**). In Experiment 2, regardless of which key the pigeon chose, the house light flashed twice per second throughout the common delay and then was extinguished. If the pigeon had chosen the right (green) key associated with the smaller, sooner reward, then when the common delay ended, the green cue light flashed once for 0.5 s and an adjusting number of pellets was delivered in the right food magazine. If the pigeon had chosen the left (red) key associated with the larger, later reward, then when the common delay ended, the red cue light illuminated for the duration of the unique delay, after which 30 pellets were delivered in the left food magazine.

In different conditions, the duration of the common delay was either 5, 10, or 20 s (plus an additional 0.5 s to allow the pigeon time to get its head down to the magazine). Within each common-delay condition, the durations of the four unique delays were the same as in Experiment 1: 2, 5, 10, and 25 s. All pigeons completed the 5-s common-delay condition first; three pigeons then completed the 10-s common-delay condition followed by the 20-s common-delay condition; the other two pigeons completed the 20-s common-delay condition first followed by the 10-s common-delay condition. In addition, four SD/LD-signal conditions (two unique delays at a 3-s common delay and two at a 5-s common delay) like those in Experiment 1 were interpolated among the CD/UD-signal conditions. Each pigeon experienced the 16 experimental conditions just described in a unique order.

At the end of the experiment, each pigeon completed a final pair of conditions. The SD/LD-signal procedure was used in the first condition of the pair and the CD/UD-signal procedure was used in the second condition. For each pigeon, the durations of the common and unique delays used in this final pair of conditions were the same as in the last CD/UD-signal condition they experienced.

Results

Figure 4 shows the amount of smaller, sooner reward equal in value to the later 30-pellet reward (i.e., the subjective value of the later reward measured in pellets available at the end of the common delay) plotted as a function of the unique delay; the 0-s common-delay condition from Experiment 1 is replotted for comparison purposes. Within each common-delay condition, the subjective

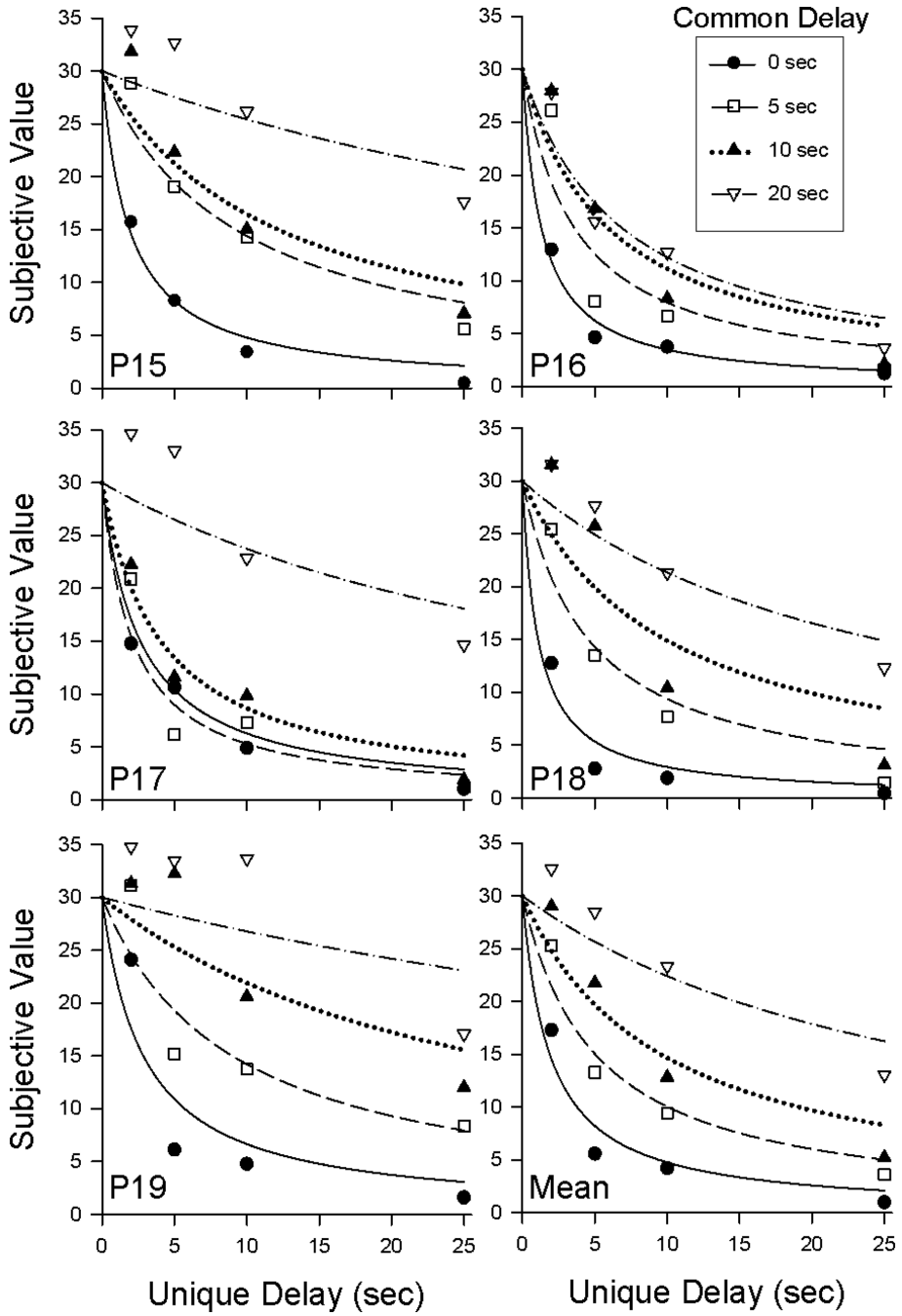

FIGURE 4 | Discounting of the larger, later reward in the 5-, 10-, and 20-s common-delay conditions in Experiment 2. The data for the 0-s common-delay condition are replotted from Experiment 1. Symbols represent subjective values (in pellets) for the four common-delay conditions. Curves represent the best-fitting discounting functions (Eq.1).

value of the larger, later reward tended to decrease with increases in the unique delay, whereas subjective value increased as the common delay was increased across conditions.

The curved lines in **Figure 4** represent Eq. 1 with D equal to the duration of the unique delay. Eq. 1 tended to provide a good description of the individual data from each common-delay condition (median $R^2 = 0.86$). As may be seen in **Table 2**, the k parameter decreased with increases in the common delay for each pigeon. This decrease in k reflects the fact that in contrast to Experiment 1, discounting in Experiment 2 became progressively shallower as the common delay increased. The difference between the results of the two experiments may be seen clearly in **Figure 5**, which shows the normalized areas under the observed subjective values (i.e., the area under the curve or AuC; Myerson et al., 2001) for each common-delay condition in Experiments 1 and 2. Areas were calculated based on the observed subjective values depicted

in **Figures 2 and 4**. Note that because they are normalized, AuC values can range between 0.0 and 1.0, with higher values indicating shallower discounting. Whereas AuC increased with the duration of the common delay in Experiment 2, reflecting a systematic decrease in the degree of discounting as predicted by Eq. 3, no such decrease was observed in Experiment 1.

Table 2 | The estimated *k* parameter and the proportion of variance in subjective values accounted for by Eq. 1 for each individual pigeon in each common-delay (CD) condition of Experiment 2.

	Common delay					
	5″ CD		10″ CD		20″ CD	
Subject	*k*	R^2	*k*	R^2	*k*	R^2
P15	0.11	0.92	0.08	0.86	0.02	0.64
P16	0.28	0.79	0.17	0.86	0.15	0.89
P17	0.47	0.95	0.25	0.93	0.03	0.65
P18	0.22	0.89	0.10	0.76	0.04	0.87
P19	0.11	0.79	0.04	0.73	0.01	0.35

Values of the k parameter were estimated by fitting Eq. 1, with D equal to the duration of the unique delay, to the data from each delay condition.

Two types of replications comparing the CD/UD procedure introduced in Experiment 2 with the SD/LD procedure of Experiment 1 were conducted in order to establish whether the shallower discounting observed in Experiment 2 at longer common delays reflected an order effect or was the consequence of the change in how the common delay was signaled. In the first type of replication, subjective values for selected unique delays from both the 3- and 5-s common-delay conditions were re-determined for each pigeon, and in all cases, the replication closely matched the original determination from Experiment 1. In the second type of replication, each pigeon completed a final pair of conditions, both with either a 10-s or a 20-s common delay, the first of which used the SD/LD signaling procedure, followed by the CD/UD procedure. The results from these two conditions, as well as those from the preceding CD/UD condition, are depicted in **Figure 6**. For each pigeon, the subjective values obtained using the CD/UD procedure were much higher than those obtained using the SD/LD procedure, demonstrating the powerful effect of explicitly signaling the common delay.

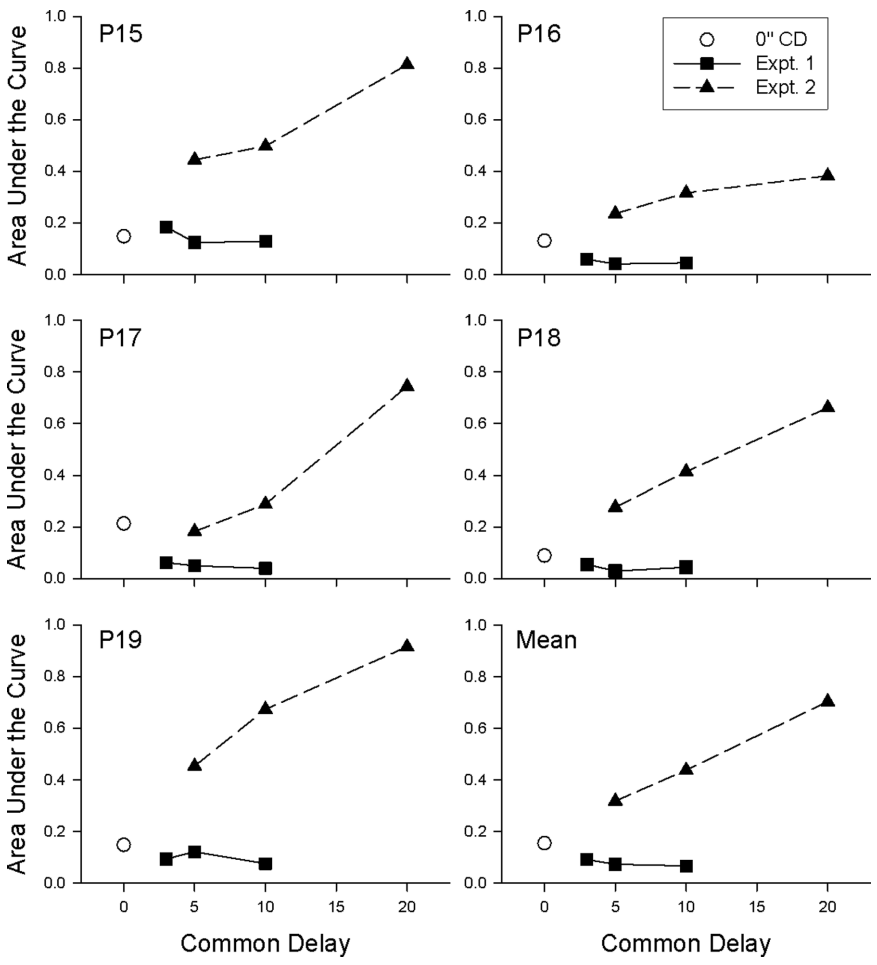

FIGURE 5 | Area under the discounting curve for each common-delay condition for each pigeon in Experiments 1 and 2. Shallower discounting is indicated by higher values.

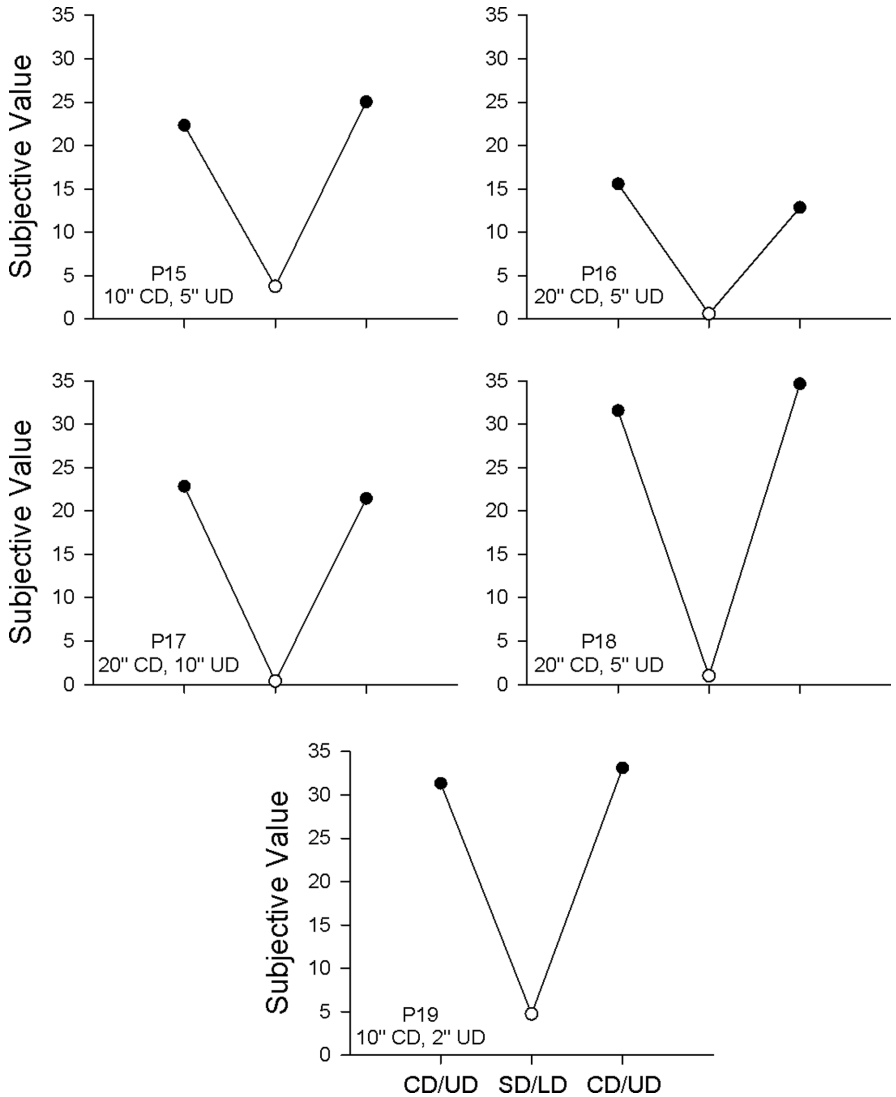

FIGURE 6 | Subjective value of the larger, later reward in the final series of replications for each pigeon in Experiment 2. CD/UD refers to the signaling procedure introduced in Experiment 2, and SD/LD refers to replications using the signaling procedure originally used in Experiment 1. Note that the common and unique delays were different for each pigeon.

In order to determine whether Eq. 3, which has only a single k parameter, will suffice to describe the systematic change in the degree of discounting across all four (0-, 5-, 10-, and 20-s) common-delay conditions, this equation was fitted to the group mean subjective values from all of the common-delay conditions simultaneously. The proportion of variance from all four common-delay conditions accounted for by Eq. 3 was then compared to variance accounted for by fitting Eq. 1 (with D equal to the duration of the unique delay) to each condition separately. Notably, Eq. 3 accounted for 91% of the variance in the data, whereas a model with four discounting parameters (i.e., one for each common-delay condition) accounted for only 2% more of the same variance, a difference that was not statistically significant [$F(3, 12) = 1.30$]. It is important to recall that even though Eq. 3 assumes a single underlying k parameter, it predicts the observed decreases in the degree of discounting because increases in the common delay produce decreases in the value of the equation's k' parameter.

Equation 3 is a special case of the discounting model, based on the common-aspect attenuation hypothesis proposed by Green et al. (2005), which describes choice between delayed rewards in humans. According to this hypothesis, the k' parameter in Eq. 3 is equal to $k/(1 + k\,w\,D_c)$, where the additional parameter w reflects differential weighting of the common delay. For humans, the value of w was less than 1.0, indicating that human participants placed less weight on the duration of the common delay than on the duration of the unique delay. In order to determine whether pigeons also underweighted the common delay, we compared the fits of Eq. 3 with k' equal to $k/(1 + k\,w\,D_c)$ when the w parameter was fixed at 1.0 with the fit when w was free to vary. Making w a free parameter did not significantly improve the fit to group mean data [$F(1, 14) < 1.0$], suggesting that pigeons (on average) do not weight the common delay differently from the unique delay.

Discussion

In the present experiment, in which the common delay was explicitly signaled regardless of which alternative (i.e., the smaller, sooner or the larger, later reward) was chosen, adding a common delay tended to decrease the degree to which the larger, later reward was discounted. Indeed, the degree of discounting decreased systematically as the common delay was increased for every pigeon. A simple hyperbolic discounting model (Eq. 3) with only one free discounting parameter, predicted the observed changes in the degree of discounting of the larger, later reward in all four common-delay conditions.

These results stand in contrast to those of Experiment 1, in which the common delay was not explicitly signaled and in which adding a common delay tended to increase the degree to which the larger, later reward was discounted. Why the addition of a common delay in Experiment 1 not only did not decrease the degree of discounting, but instead actually increased discounting, is puzzling. One possibility is that by making the delay to the larger reward even longer, the common delay made the signal for the larger, later reward (i.e., the red light) more aversive. Of course, adding a common delay also increased the delay to the smaller, sooner reward, but it is possible that, as is the case with observing stimuli, the stimulus that signals the longer wait to primary reinforcement is a conditioned punisher just as the stimulus that signals the shorter wait is a conditioned reinforcer (e.g., Fantino, 1977; Dinsmoor, 1983).

Regardless of the mechanism underlying the extremely steep discounting in Experiment 1, the difference between the results of the two experiments is clearly due to the difference in the stimuli that were associated with the common delay. This may perhaps be most clearly seen in the results of the final experimental manipulations (see **Figure 6**), in which the signaling procedure of Experiment 1 was reintroduced. In every case, this manipulation markedly increased the degree of discounting, which returned to its previous level when the signaling procedure of Experiment 2 was reinstated. These results suggest that pigeons' discounting is controlled not just by the choice alternatives, but also by the way in which the choice is framed.

The effect of explicitly cueing the common delay in Experiment 2 is reminiscent of the effect of explicitly cueing the post-reward interval on discounting in rhesus macaques (Pearson et al., 2010). In the monkey study, explicit cueing reduced the degree of discounting relative to a condition in which the post-reward interval was uncued, again indicating that the way in which questions are framed may have significant effects on animals' choices.

The question of major interest in the present study was whether the hyperboloid discounting model describes pigeons' choices between two delayed rewards just as it describes humans' choices. Indeed it does, at least under the conditions studied in Experiment 2. This is not to say that there are no differences. Green et al. (2005) reported that humans, on average, underweight the common delay when choosing between two delayed rewards. In contrast, pigeons in the current experiment, on average, weighted both the common and unique portions of the delay to the larger, later reward equally. Taken together, the results of Experiment 2 reveal both similarities and differences between discounting by pigeons and humans. Although the two species appear to differ in whether or not equal weighting is given to the common and unique portions of the delays, their behavior is similar in that when the common portion of the time until delayed rewards is increased, the degree of discounting decreases.

GENERAL DISCUSSION

In two experiments, pigeons were given choices between two delayed food rewards, a smaller amount available sooner and a larger amount available later. In Experiment 1, the delay common to both rewards was not explicitly signaled. Compared to choice between an immediate and a delayed reward, the addition of a common delay resulted in an increase in the degree to which the later reward was discounted. In contrast, when the common delay was explicitly signaled in Experiment 2, the extent to which the larger, later reward was discounted decreased systematically as the common delay was increased. The fact that differences in the signaling of the delays could have such a marked effect on the degree of discounting, even though the procedures were otherwise the same, highlights the important role that signaling plays in discounting in particular and reinforcement processes in general (Lattal, 2010).

COMPARISONS OF DIFFERENT DISCOUNTING MODELS

The pattern of shallower discounting with increases in the common delay observed in Experiment 2 is similar to what has been observed in humans (Green et al., 2005). It is inconsistent, however, with what would be predicted based on exponential or quasi-hyperbolic models of discounting. Exponential discounting assumes that the subjective value of a delayed reward decreases by a constant proportion with the passage of each additional unit of time; quasi-hyperbolic discounting that the subjective value of a delayed reward is unaffected by the passage of just a single time period, but decreases exponentially thereafter (Laibson, 1997).

If discounting were exponential, and people and other animals made choices between delayed outcomes by comparing their present (i.e., discounted) values, then the degree of discounting would be unaffected by the duration of the common delay. Similarly, if discounting were quasi-hyperbolic, then once the time until the smaller, sooner outcome exceeded one time period, then the degree of discounting would be unaffected by further increases in the common delay.

In contrast, the present discounting framework, which assumes that choices are made based on comparison of the present subjective values of hyperbolically discounted outcomes (as instantiated in Eq. 3), correctly predicts the observed pattern of results in Experiment 2. As predicted, increases in the common delay resulted in decreases in how steeply the later reward was discounted as a function of the unique delay. As the time until the sooner reward (i.e., the common delay) was increased, the degree to which the subjective value of the later reward decreased, relative to that of the sooner reward, decreased. This decrease was reflected in the amount of sooner reward that was equivalent in subjective value to the later reward. Importantly, a mathematical model (Eq. 3) that assumed only a single, fundamental discounting parameter predicted the observed changes in the degree of discounting of the larger, later reward as measured in terms as the amount of smaller, sooner reward of equivalent value.

IMPLICATIONS FOR SPECIES COMPARISONS

The present effort provides a cautionary tale for those making species comparisons. What initially appeared to be a clear species difference (i.e., the addition of a common delay, which leads to shallower discounting in humans, led to steeper discounting in pigeons) turned out to be peculiar to the way in which the choice

was framed. That is, the way in which the common portion of the delays to smaller, sooner and larger, later rewards was signaled turned out to determine the way in which pigeons chose between delayed rewards. When the common delay was made more salient, pigeons' choice behavior resembled that of humans choosing between delayed monetary rewards, although the time scale differed by orders of magnitude. We would point out, however, that recent studies reveal that this apparent species difference in scale breaks down when the choices presented to human and non-human animals are framed in more similar ways. That is, the subjective value of directly consumable rewards declines over seconds in deprived humans (Jimura et al., 2009, 2011) just as it does in deprived non-human animals (Mazur, 2000; Green et al., 2004).

We do not contend, however, that these discounting rates are representative of foraging in the natural environment (Stephens et al., 2004), either for humans or other animals. For laboratory experiments, researchers have designed tasks that allow them to examine discounting rates while holding the time between choice opportunities constant, regardless of how representative such situations are of those encountered in the natural environment. Discounting as observed under such circumstances is only one aspect of what determines choice behavior in the natural environment, but it presumably does play a role, and tasks like those in the present study are designed to allow examination of the discounting process in relative isolation.

The focus of the present study, however, was not on the role that discounting plays in foraging, although this is an important (and controversial) issue (e.g., Stephens et al., 2004; Kalenscher and Pennartz, 2008). Rather, the question here was whether the hyperboloid discounting model that describes human choices between two delayed rewards would also describe pigeon choices when both species are tested under somewhat analogous circumstances. And indeed, in Experiment 2, when the procedure used in Experiment 1 was modified so as to make more salient the variables that the model assumes control human discounting, the hyperboloid discounting model did describe pigeon choices.

The present findings also demonstrate how research with human and non-human animals can be mutually informative and, as such, are consistent with the view that species comparisons can increase our understanding of human decision making (Hackenberg, 2005; Shettleworth, 2010). Although the results of Experiment 1 suggested striking differences between humans and pigeons with respect to their choice between delayed rewards, consideration of recently proposed models of human discounting (Green et al., 2005) suggested critical procedural changes that were made in Experiment 2. The results observed with this modified procedure, in turn, revealed fundamental similarities between pigeons' and humans' choice behavior. More specifically, the present findings extend the generality of the hyperboloid discounting model and provide interspecies support for the hypothesis that choice between delayed outcomes is based on comparison of their hyperbolically discounted present values.

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Social facilitation revisited: increase in foraging efforts and synchronization of running in domestic chicks

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Social influences on foraging efforts were examined in domestic chicks by investigating the frequency of runs made to feeders and the amount of pecking to gain food. Single or paired chicks foraged in an I-shaped maze equipped with a millet feeder on each end, that distributed one or two grains at variable intervals. Regardless of when the grain(s) were dispensed, chicks ran back and forth between the feeders. Analyses of their movement patterns revealed: (1) running patterns were not directly synchronized with the dispensing of grain(s), (2) running distance was longer in paired chicks than in single chicks, (3) paired chicks partially synchronized their runs between feeders, and (4) social effects were immediate but cumulative after repeated blocks. We further examined the social effects on running by dividing the I-maze into two parallel lanes separated by a transparent wall, so that *kleptoparasitic* interference of food did not occur. Again, the chicks increased their running speed and were even more synchronized with their partner's movements, indicating that food competition alone was not responsible for increased foraging effort. The number of pecks to get grains was also assessed under conditions where the food tray was gradually replaced, from an easy one to more difficult ones. When tested in the separated I-maze, paired chicks pecked more in the difficult food situation without increase in the number of gained grains. Results suggest that (i) social facilitation leads to increased foraging efforts and (ii) the presence of a conspecific is alone may lead to enhanced foraging efforts in chicks. These findings are discussed in terms of possible ecological background of social facilitation.

Keywords: work, cost, handling, consumption, competition, social foraging, kleptoparasitism

INTRODUCTION

Social facilitation, which results in an enhancement of behavioral performance or an increase in work investment when an individual is in the presence of one or more conspecifics, has been widely reported in a variety of animals including humans (Zajonc, 1965 for a review), e.g., ants building a nest (Chen, 1937), cockroaches running in mazes for food (Gates and Allee, 1933), hyenas in drinking behavior (Glickman et al., 1997), and humans engaged in physical work (Triplett, 1898) or mental work (Allport, 1920), leading to recent report on physiological characteristics of the facilitation in cardiovascular responses (Blascovich et al., 1999). While many diverse taxa exhibit socially facilitated behavior, surprisingly little is known about the ecological contexts in which social facilitation occurs.

From an ecological standpoint, social interference by conspecifics is considered an important factor in influencing an individual's foraging strategies. Classical foraging theory typically focuses on the perspective of a single forager (Charnov, 1976); however this neglects the overall interactions that occur in group-living animals. A more recent perspective, coined the "Social Foraging Theory," suggests that not only individual decision-making, but also conspecific behavior, influences the outcome of an individual's foraging success (Giraldeau and Caraco, 2000). For example, Parasitic Jaegers (*Stercorarius parasiticus*) will forage in larger groups when engaging in risky behavior such as attacking and steeling fish from Common Terns (*Sterna hirundo*), even though they could gain more food by foraging in smaller groups or by themselves (Bélisle, 1998). Bélisle (1998) argued that the risk of starving must also be included in foraging theory in addition to such things as net/gross intake rate or efficiency, since group formation is expected to reduce variance of the food-encounter rate.

In behavioral studies using chicks, Tolman and Wilson (1965) reported that paired chicks consumed a larger amount of food than did isolated chicks only when the chicks had been deprived of food. However, their study failed to show conclusive results on the effects of social facilitation on rates of pecking (Tolman, 1967). Tolman and Wilson (1965) also did not control the amount of food chicks could consume, thus it was uncertain whether the increased consumption was a result of the amount of food available rather than mere social facilitation. In our study, we tried to know whether social facilitation could improve individual pay-off [i.e., rate of net gain = (benefit − work cost)/time], or otherwise other currency (e.g., low probability of starvation; Caraco et al., 1980) should be considered.

In the present study, we examined the influence of social facilitation in 1 to 2-week-old domestic chicks (*Gallus domesticus*). By strictly controlling the amount of food delivered, we examined whether foraging competition (i.e., reduction of gain by interference of other individuals) may socially facilitate an increase in the amount of foraging efforts in chicks. Chicks provide a unique opportunity

for studying the neuroscience of decision-making in relation to behavioral ecology and economics (Matsushima et al., 2003, 2008 for reviews), because we can quantitatively control feeding conditions and potential energy budgets in experiments. Furthermore, chicks are precocial animals that begin to forage independently as soon as they hatch, and so individual development can be controlled as well. In our study, we investigated two foraging behaviors, running, and pecking, in order to assess whether foraging efforts would increase under specific social conditions (i.e., social facilitation). Running to, or approaching food, and pecking at, or handling, food have already been shown to have distinct neural substrates involved (ventral striatum/nucleus accumbens and arcopallium, respectively; Matsushima et al., 2008). For example, lesions of the ventral striatum enhanced choices of small/immediate reward against large/distant alternative (Izawa et al., 2003; Aoki et al., 2006a). Similarly, lesions of the arcopallium caused chicks to choose the small/easy reward more frequently than the large/costly alternative (Aoki et al., 2006b). It is therefore possible that social facilitation can occur differently in these two aspects of foraging effort.

MATERIALS AND METHODS

SUBJECTS

All experiments were conducted under the guidelines and approval of the Committee on Animal Experiments of Hokkaido University. The guidelines are based on the national regulations for animal welfare in Japan (Law for Humane Treatment and Management of Animals; after a partial amendment No. 68, 2005). After the experiments, chicks were sacrificed in carbon dioxide according to the guidelines.

A total of 99 male domestic chicks (*G. domesticus*, White Leghorn strains) were used. New hatchlings (post-hatch day 1: presumed hatching day) were obtained from a local supplier (Hokuren Central Hatchery, Iwamizawa, Hokkaido, Japan). Chicks were paired and housed in transparent plastic cages (15 cm × 28 cm × 12 cm) under white lighting (12L: 12D; light period starting at 08:00) and thermo-controlled at ca. 30°C. Pairs of chicks in the same cages were trained and tested in the same conditions.

Two types of food were given, grains of millet and chick mash food. The total amount of food per day was kept at a certain level so that (1) the body weight of chicks gradually increased and (2) the chicks actively consumed food during experiments. From post-hatch day 2, chicks were fed mash food. The amounts of mash food were 1 g (post-hatch days 2–5), 1.5 g (days 6 and 7), and 3 g (from day 8). From post-hatch day 3, grains of millet were added. The amounts of grains (per chick per day) were 1 g (day 3), 2 g (day 4), 3 g (day 5), 2.5 g (days 6 and 7), and 2 g (from day 8). Until day 3, all chicks were communally fed. From day 4, chicks were allocated to a communally fed condition or solitarily fed condition depending on experiments: varied among groups in Experiment 1 and solitarily in Experiments 2 and 3. In the groups of solitarily fed chicks, each individual was fed in a cage that was visually separated by a black plastic wall, so that chicks did not see the other chicks eating food; these chicks were communally housed except when the daily diet was given.

APPARATUS

In Experiment 1, an I-shaped maze equipped with one-lane (1-lane maze; 12 cm in width, 88 cm in length and 30 cm in height) was used (**Figure 1A**). The maze was equipped with a pair of terminal feeders.

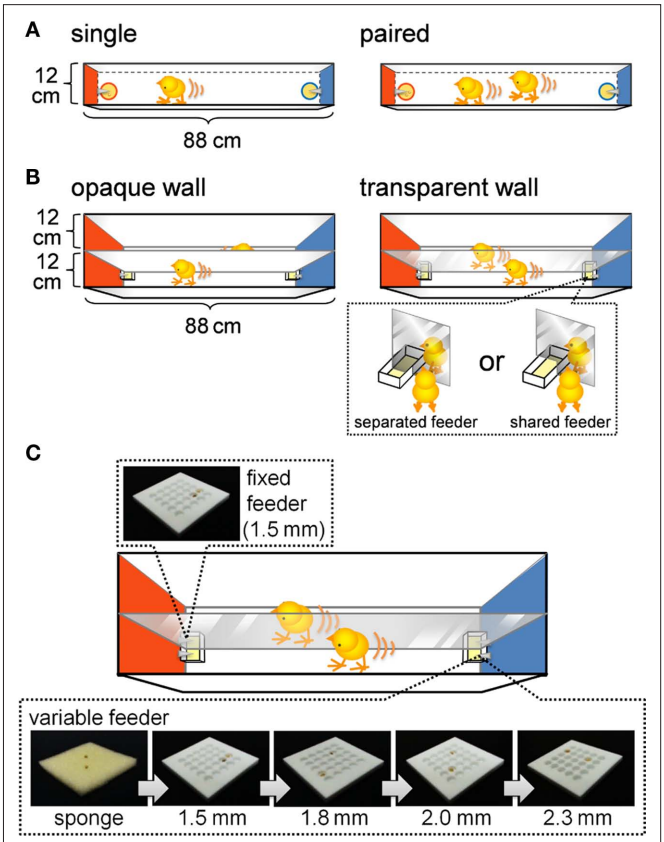

FIGURE 1 | Experimental apparatus for examining foraging efforts, running distance (A,B), and number of pecks (C). (A) One-lane I-shaped maze equipped with a pair of terminal feeders. Terminal walls of the maze were colored red and blue. The feeders supplied grains of millet according to a variable interval schedule. One grain was supplied at one time in the single-chick condition (left), and two grains were supplied at one time in the paired-chicks condition (right). Note that the paired chicks were competing over food, whereas the single chicks were not. **(B)** Two-lane I-shaped maze. Chicks and feeders were separated by an opaque (left) or a transparent (right) wall. In the transparent wall condition, the feeders were either separated or shared. Note that the paired chicks in the shared feeder condition were competing for food, whereas chicks in the other condition did not. **(C)** The 2-lane maze was equipped with a fixed feeder and a variable feeder. The food tray of the fixed feeder was made of a plastic plate with 25 holes (5 × 5), each 1.5 mm deep. The food tray of the variable feeder was either a sponge or plastic plates of variable depth (ranging from 1.5 to 2.3 mm). Supplied grains tumbled into the holes, making it difficult for chicks to obtain the grains. The deeper the holes were, the more difficult it was for chicks to obtain the grains. Trays of the variable feeder were sequentially replaced in an order from the easy sponge to the more difficult plates every ca. 3 min. See text for details.

Walls at the terminals were colored red (left) or blue (right). Each feeder supplied a grain of millet food at variable intervals. Plastic Petri dishes (5.5 cm in diameter to a depth of 1.5 cm) were used as food trays, and the floor of each dish was covered with sponge.

In Experiment 2, an I-shaped maze equipped with two lanes (2-lane maze; 25 cm in width, 88 cm in length, and 40 cm in height) was used (**Figure 1B**). These two lanes had the same width as that of the 1-lane maze used in Experiment 1 but were separated by a transparent acryl board in one groups of chicks. In another group, in order to visually separate the two lanes, opaque white cardboard was

attached to both sides of the acrylic board so that the chicks could not see each other. On each terminal feeder, two food trays were placed in adjacent positions over the separation board. Rectangle-shaped food trays (3 cm in width, 4 cm in length, and 2 cm in depth) with sponge on the floor were use. In the shared feeder condition, a 4-cm-wide window was opened on each terminal end of the separation board, and the chicks in both lanes shared the food supplied to a food tray (6 cm in width, 4 cm in length, and 2 cm in depth) placed at the center.

In Experiment 3, the same 2-lane maze as that in Experiment 2 was used after a slight modification to the food trays (**Figure 1C**). Square food trays (width and length of 3.6 cm depth of 1.8 cm) were used with two different types of floor coverage: one with sponge and the other with acrylic plates with 25 holes in the surface (aligned in 5×5, 4 mm in diameter). Four different types of acryl plates were used with different depths of the holes: 1.5, 1.8, 2.0, and 2.3 mm. Food trays were manually replaced, and a single replacement took ca. 10 s.

In all experiments, in order to prevent chicks to associate the feeder sound with food reward, sounds of electric motors were replayed at variable intervals from instruments placed around the apparatus; the mean interval was set at 2.5 s, uniformly distributed from 1.5 to 3.5 s. The apparatus was placed in a dark room kept at ca. 25–30°C and illuminated by four 60 W white light bulbs placed above the runway and feeders. Timing of grain delivery and the noise sound were controlled by microrobots (RCX, LEGO Mindstorms). Behavior of the chicks was recorded by a video recorder (DCR-SR65, Sony, Japan) and color CCD cameras (250 k pixels with NTSC output), and the recordings were stored for offline analysis.

BEHAVIORAL PROCEDURES

In Experiments 1–3, chicks were initially habituated to the experimental maze according to a common procedure for two successive days (pre-1 and pre-2) on post-hatch days 6–15. For habituation, paired chicks (housed in the same cages) were placed on the midway part of the maze in which some food (ca. 100 grains) was given in advance. After the chicks had consumed the food, feeders started to deliver grains by the same procedure as that used in each experiment. Two successive habituation sessions (ca. 20 min in total) were given per day for each of pre-1 and pre-2 except for Experiment 3, in which one long session of habituation (ca. 20 min) was given instead. The experimental data were obtained after the habituation.

Experiment 1: effects of paired foraging on approaching food, an inter-group comparison in the 1-lane maze

Effects of paired foraging in the maze and the cage were examined in regards to subjects' distance and synchrony during running. Running distance was used to calculate the rate of approaching food at either end of the I-maze, where an increase in distance corresponds to increased running during the experimental condition.

"Paired in the maze" means that chicks foraged in pairs at the test, whereas "paired in the cage" means that the chicks foraged in pairs in the housing cage, in which main diet (mixture of mash food and millet) was supplied (**Figure 3A**).Chicks were thus divided into four conditions: (1) paired in the maze/paired in the cage, (2) paired in the maze/single in the cage, (3) single in the maze/paired in the cage, (4) single in the maze/single in the cage.

After the habituation (pre-1 and pre-2), experiments were conducted for five consecutive days (days 1–5) and chicks received one test session per day. In each of the sessions, after a short habituation period in the maze (i.e., 1 min after the chick had consumed all of the food available, namely, 20 grains/chick placed in advance in each feeder), each of the two feeders supplied one grain at a time with variable intervals (mean interval of 15 s, uniformly distributed in a range of 10–20 s). In a single session, the programmed food delivery continued 30 times and thus lasted for ca. 8 min. The chicks were then left in the maze for an additional 2 min after they had consumed all of the grains delivered on the food trays, and the test session of the day was terminated.

In the I-shaped maze, the following two parameters were measured: (1) running distance (or how far the chick ran) and (2) synchrony index. Synchrony index was defined as the ratio of time in which both chicks stayed in the same side of the maze, shown as percentage of the total time recorded. The position of each chick's head was automatically and unequivocally given by computer-based video analysis, as either being placed on the red or the blue side of the maze. When both chicks were always in the same end, the synchrony index was 1.0 (in-phase synchrony). When, on the other hand, chicks were in opposite ends, the index was 0.0 (anti-phase synchrony). When both chicks moved in a random and independent fashion, the index would show a chance level of 0.5 (asynchrony).

Experiment 2: effects of paired foraging on approaching food, an inter-group comparison in the 2-lane maze

In order to differentiate food competition from social facilitation by a nearby conspecific, we removed the factor of food competition by separating paired chicks with either a transparent or an opaque partition down the middle of the maze's track, thus creating two separate lanes (**Figure 1B**). After the habituation (i.e., paired foraging in the maze on pre-1 and pre-2), similar to Experiment 1, test sessions were repeated five times, one session per day (days 1–5). Each of the two feeders supplied one grain at a time with variable intervals (mean interval of 15 s, uniformly distributed in a range of 10–20 s). In a single session, the programmed food delivery continued 30 times and thus lasted for ca. 8 min. The following two parameters were measured: (1) running distance and (2) synchrony index.

Effects of paired foraging on running distance, an intra-individual comparison

The immediate effect of paired foraging was examined in terms of running distance. A group of chicks (post-hatch days 12–14) were re-used after Experiments 1 and 2 (see above); chicks that had been solitary fed in both the maze and the cage were used. Immediately after each chick had been individually placed in the maze, both feeders delivered grain 10 times at variable intervals (mean interval of 15 s, uniformly distributed in a range of 10–20 s, 1 grain per delivery); this term is referred to as the *first "single" phase*. The companion chick was then introduced into the maze, and the feeders delivered twice as much grain (2 grains per delivery) 10 times; this term is referred to as the second *"paired" phase*. In the third phase, the companion chick was removed from the maze, and the subject chick received feeding another 10 times. Each phase lasted for ca. 3 min.

Experiment 3: effects of paired foraging on approaching and pecking at food, an inter-group comparison in the 2-lane maze

Effects of visual perception of the other chick on running (i.e., approaching food) and on food pecking (handling food) were examined in the 2-lane maze. The food tray difficulty (estimated on the basis of the number of pecks required for chicks to gain a certain amount of grain) was controlled by systematically changing the types of acryl plates used as the floor of the feeder (**Figure 1C**). After habituation (i.e., paired foraging in the maze on pre-1 and pre-2), similar to Experiments 1 and 2, test sessions were repeated three times, one session per day (days 1–3); chicks were left untested for 4 days between test days 1 and 2. Each of the two feeders supplied two grains at a time with variable intervals (mean interval of 30 s, uniformly distributed in a range of 20–40 s).

In the tests, the variable feeder initially had a sponge floor. When the variable feeder had delivered six times (12 grains), the sponge was replaced by an acryl plate with 1.5-mm-deep holes. The 1.5-mm plate was subsequently replaced by 1.8, 2.0, and 2.3 mm plates when the variable feeder had delivered 12 grains for each plate. Four CCD cameras were set just above the feeder to record pecking behavior of the chicks were video recorded. The following four parameters were measured: (1) number of pecks, (2) number of gained grains, (3) running distance and (4) velocity. Velocity (cm/s) was measured in the runway except for the areas near the feeders (<10 cm from the walls).

DATA ANALYSIS

Recording and analyzing approaching behavior

Experiments were videotaped and coded later at rate of 30 frames per second using a Handycam recorder. The Handycam was located directly above the I-maze during testing, providing an aerial view of the subjects and apparatus. Chicks were individually marked by a rectangular piece of fluorescent-colored tape (Yamato Co., Ltd., Japan) affixed to their heads. The position of the fluorescent markers was analyzed by using Move-tr/2D 7.0 software (Library Co., Japan) and the trajectories and running distances were thus calculated.

Statistical analysis of generalized linear mixed model

The following five types of behavioral parameters were analyzed by using R for the platform of statistic calculation: running distance, synchrony index, number of pecks, number of gained grains and velocity. See Appendix for details.

RESULTS

Once habituated, chicks began to actively run between the terminal feeders as soon as they were put in the maze, even without any visual cues. Furthermore, the runs were not in response to the timing of food delivery. Singly tested chicks stopped running within ca. 1 min of the final delivery of food items. We therefore assumed that running distance of the runs represented "approaching effort" and pecks at the feeders represented "handling effort," rather than reflexive responses to food, and examined food-approaching behaviors in a series of experiments.

EXPERIMENT 1: PAIRED FORAGING INCREASED RUNNING DISTANCE

Paired chicks ran more than single chicks did. **Figure 2A** shows representative running trajectories of single (top and second records) and paired chicks (third and fourth records) at tests. Runs by single chicks were irregular on day 1 (top record), but they were more regular and more active on day 5 (second record). Runs by paired chicks were highly synchronized on day 1 (third record), but they were unsynchronized on day 5 (fourth record). Superimposed trajectories (**Figure 2B**), however, showed that the runs were not in response to the timing of food delivery.

Paired foraging in the maze, but not in the cage, increased running distance and synchrony index. A comparison of running by the four groups of chicks (n = 10 in each groups) is shown in **Figure 3B**. Based on running distance, AICs were calculated for each of the eight models in which the variables of *day* (1–5), *maze* (paired or single), and *cage* (paired or single) were considered (See **Table A1** in Appendix for details). Of these models, the *day-maze* model yielded the smallest AIC. The *day-maze-cage* model yielded the same-AIC, but the *cage* term was not reliable for its coefficient (p = 0.197). Similarly, based on the synchrony index, AIC calculations revealed a facilitating effect of paired foraging in the maze, but

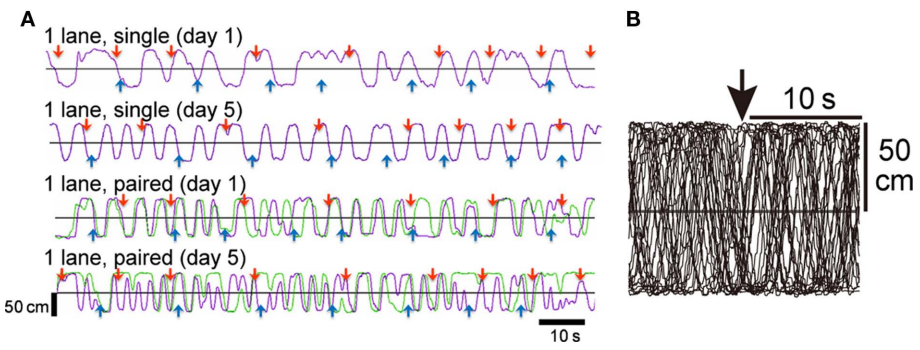

FIGURE 2 | Representative running trajectories in the 1-lane condition (Experiment 1). (A) Two minutes records of running trajectories. Purple and green lines represent the trajectory of individuals along the long axis of the maze; upward indicates the direction to the red feeder. Red and blue arrows indicate the time at which a grain(s) was delivered. The top and second records (1-lane, single) were obtained from the same chick on different days (days 1 and 5). The third and fourth records (1-lane, paired) were obtained from a pair of individuals. Comparison of the trajectories on day 1 (top vs. third) and day 5 (second vs. fourth) clearly shows that the paired chicks ran at a higher frequency. **(B)** Thirty superimposed trajectories aligned at the time of grain delivery from the red feeder (downward arrow at the top). An example obtained from a chick tested in the single condition in the maze. Note that the runs were not in response to the food delivery.

not those of paired foraging in the cage (**Table A2** in Appendix). We therefore concluded that the presence of other chicks and/or food competition among paired chicks could have caused the increase in approaching effort. It is not clear whether synchronization might be directly (and causally) linked to the increased effort.

EXPERIMENT 2: VISUAL PERCEPTION OF THE OTHER CHICK, BUT NOT FOOD COMPETITION, EXCESSIVELY INCREASED RUNNING DISTANCE

To reveal the cause of the increased running distance, we separated the maze into two lanes by a transparent/opaque wall (see **Figure 1B**), and we found that visual perception increased both running and synchrony indexes. **Figure 4** shows representative trajectories obtained from one pair in each group. When separated by an opaque wall, chicks in the 2-lane maze (therefore with no food competition) ran back and forth between feeders independently (top record in **Figure 4**). When visually interacting via a transparent wall, chicks ran back and forth in high synchronization (second record). Direct foraging competition at shared feeders (see **Figure 1B**, bottom) did not result in difference from when the transparent wall separating the feeders was present (compare second and bottom record in **Figure 4**). It is notable that a high degree of synchrony was maintained until day 5, in contrast to the unsynchronized running seen in Experiment 1 (see **Figure 2A**, fourth record, and **Figure 3B**, bottom).

Based on the running distance and synchrony index (**Figure 5**), AICs were calculated for eight models. As variables, *day* (1–5), *wall* (whether the wall was transparent or opaque), and *feeder* (whether the feeders were separated or shared) were considered (**Table A3** in Appendix). For running distance, the *day-wall* model yielded the smallest AIC (16191). The *day-wall-feeder* model gave rise to the second-smallest-AIC (16192), but the *feeder* term was not reliable for its coefficient ($p = 0.2921$). For synchrony index (**Table A4** in Appendix), the *day-wall* model yielded the smallest AIC, but the *day* term was not reliable for its coefficient ($p = 0.0844$); thus, the result is different from the synchrony index in Experiment 1, in which the coefficient of the *day* was negative. We therefore tentatively conclude that the running distance and synchrony index are not linearly linked. Increased effort is not brought about by changes in synchronized running.

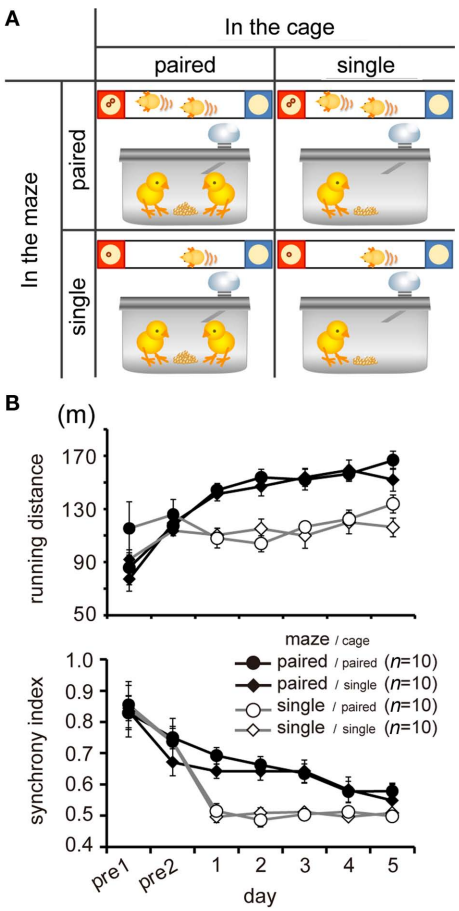

FIGURE 3 | Paired foraging in the maze, but not in the cage, influenced running (Experiment 1). (A) Chicks were divided into four experimental groups according to 2 × 2 block placement. "In the maze" means chicks were single or paired in the I-shaped maze during the tests, whereas "in the cage" means that chicks foraged in single or paired condition in their home cage. Note that chicks were housed in pairs in all conditions except foraging. **(B)** Means (±SEM) of running distance (upper) and synchrony index (lower) during feeding time (ca. 8 min) are plotted against the day of the experiment. Open and filled symbols denote paired and single foraging in the maze, whereas circles and rhombi denote paired and single foraging in the cage, respectively, in this and the following figures.

PAIRING IMMEDIATELY INCREASED RUNNING DISTANCE

In both Experiments 1 and 2, difference in running distance between the groups appeared from day 1 of the experiment. In order to determine whether paired foraging could immediately increase the approaching effort, we examined running distances by an intra-individual comparison. As shown in a typical example (**Figure 6A**), pairing immediately increased running. The average running distance for each condition (mean ± SEM, $n = 14$) is shown in **Figure 6B**. The Wilcoxon signed-rank test revealed a significant difference between paired phase and mean of the first and last phases ($T = 2$, p-value = 0.0003662).

EXPERIMENT 3: PAIRING INCREASED PECKS WITHOUT IMPROVED FOOD GAIN

In order to determine whether paired chicks also increased their handling effort (i.e., efforts to collect food), we examined rates of pecking for food by using a series of trays that modified the

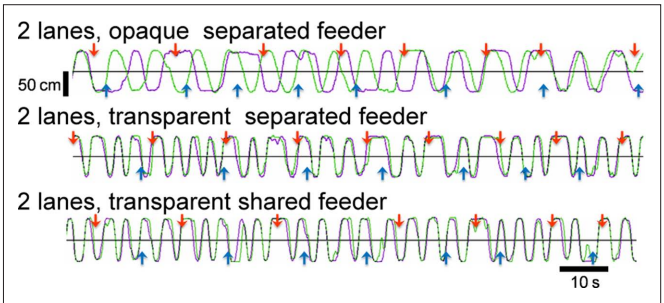

FIGURE 4 | Representative running trajectories in the 2-lane condition (Experiment 2). When separated by an opaque wall, running trajectories were not synchronized (top). When separated by a transparent wall, runs were more frequent and synchronized regardless of whether the feeder was separated (middle) or shared (bottom). All records were obtained on experimental day 5.

difficulty for food collection (**Figure 1C**). Paired chicks increased the number of pecks, particularly in the difficult food condition (in a range from 1.8 to 2.3 mm; **Figure 7A**). The number of grains decreased in accordance with increased difficulty of food tray, but the number of grains was not different between the single and paired groups (**Figure 7B**). Running distance was greater for paired chicks as found in Experiments 1 and 2, but the difference gradually diminished in the difficult food condition (**Figure 7C**). However, the velocity at which paired chicks ran remained consistently higher than in the single chicks (**Figure 7D**). The running distance of paired chicks decreased not because they ran slowly but because they stayed at the feeders for a longer time.

For all of the data shown in **Figures 7A–D**, AICs were calculated for five models in which the variables of *feeder* (food tray difficulty, five steps ranging from sponge to 2.3 mm), *maze* (paired or single), and their *interaction* were considered (**Tables A5–A8** in Appendix). For the number of pecks, the *feeder–maze-interaction* model yielded the smallest AIC (**Table A5** in Appendix), indicating that the effects of pairing emerged on handling effort only when the food was difficult to obtain. For the number of grains, on the other hand, the *maze* term was not included in the chosen model (**Table A6** in Appendix), indicating that the paired and single chicks had similar gains. For running distance, the *feeder–maze-interaction* model was chosen (**Table A7** in Appendix). The *interaction* term suggested that the difference between the paired and the single chicks were smaller for the more difficult food trays. For velocity, the *maze* model was chosen (**Table A8** in Appendix).

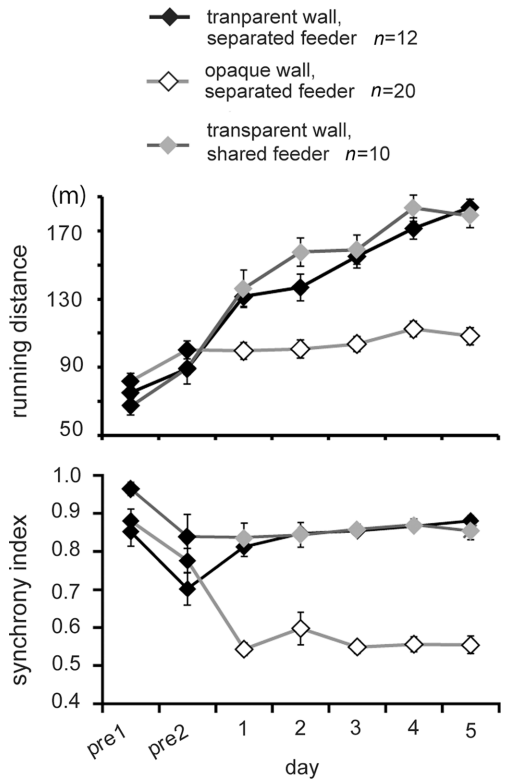

FIGURE 5 | Social interactions via the transparent wall caused a high degree of synchrony regardless of foraging competition (Experiment 2). Means (±SEM) of running distance (upper) and synchrony index (lower) are plotted against the day of the experiment. Open and filled symbols denote data in the opaque wall and the transparent wall, respectively. Gray symbols denote the data obtained from another group in which the feeders were shared and the wall was transparent.

DISCUSSION

ECOLOGICAL ACCOUNTS OF THE EXCESSIVE FORAGING EFFORTS

In this study, we found that visual perception of other individuals, rather than direct foraging competition, increased foraging efforts for approaching food (running distance) as well as for handling food (number of pecks). Increased foraging efforts in this study appear to be a result of social facilitation. Zajonc (1965) argued that social facilitation affects "dominant responses," meaning that dominant (or well-developed) action patterns are most likely to be socially enhanced. Both running and pecking are well-developed behaviors in actively foraging domestic chicks. It should be noted, however, that chicks never exhibit running or pecking behavior when food is not available (data not shown), indicating that direct inter-individual interactions alone failed to cause social facilitation. It should also be noted that the term "social facilitation" is a psychological label, never specifying its functions in terms of economics/ecology. The idea of social facilitation is therefore not mutually exclusive with the idea of work investment under competition.

Our results suggest that currencies (or value functions) other than the food benefit are critical in social facilitation, in accordance with social foraging theory. According to Koops and Giraldeau (1996), starlings adopt foraging tactics that minimize the probability of energetic shortfall rather than maximize mean intake rate (or the benefit). Chicks may also make use of other individuals'

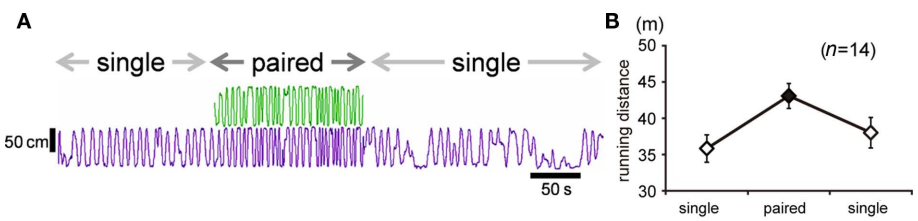

FIGURE 6 | The run was facilitated as soon as a companion chick was introduced (Experiments 1 and 2). (A) Representative running trajectories of a pair of chicks. Subject chick (purple) received 30 deliveries of food, divided into three phases. In the first phase, the subject was tested in single condition. In the second phase, a companion chick (green) was introduced into the maze. In the third phase, the subject was again tested in single condition. Each phase lasted for ca. 3 min. **(B)** Means (±SEM) of running distance recorded in the first and third phases of the single condition (open symbols) and in the second phase of the paired condition (filled symbol).

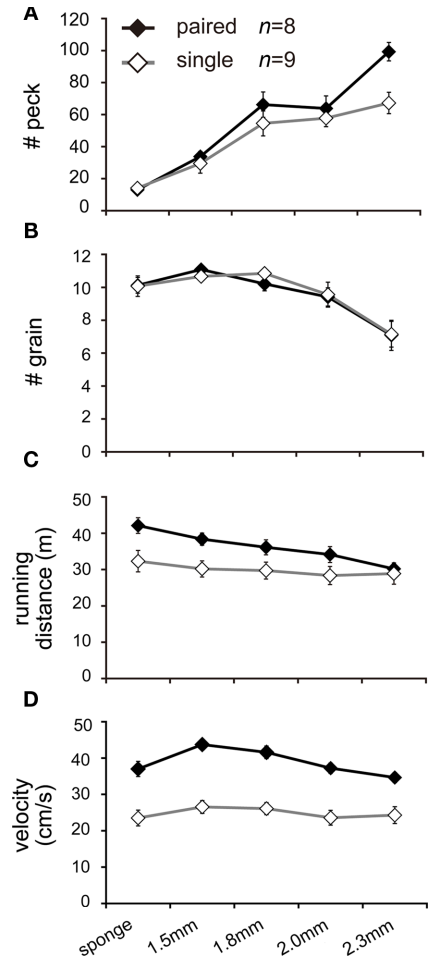

FIGURE 7 | Social interactions of pairing were also found in the number of pecks (handling effort), particularly in the difficult food condition (Experiment 3). Means (±SEM) of two groups of chicks [paired (filled symbols) and single conditions (open symbols)] are plotted against the phases of different food tray difficulty (from the sponge to the plate with deep holes). Each individual chick was repeatedly tested on three successive days, and the values were averaged to yield individual data. Number of pecks **(A)**, total gain of grains **(B)**, running distance **(C)**, and mean velocity **(D)** are plotted. Note that the chicks spent a shorter time for running but ran at higher velocity in the paired condition, even in the difficult condition.

information at food sites to avoid the risk of starvation, given that chicks have been shown to be risk-averse to food quantities (Kawamori and Matsushima, 2010). However, much remains to be discussed about whether excessive running and pecking was really "inefficient," since we were not able to calculate the energetic cost of running and pecking in terms of joules/calories. It is still possible that running and pecks are energetically very cheap and that the overt investments found in this study do not cause a negative energetic budget. Precise measurements of physical expenditures for running and pecking actions are needed.

Excessive foraging efforts found in this study might also lead to impulsive choices. Amita et al. (2010) reported that repeated experience of competitive foraging for a few days resulted in a higher level of choice impulsivity, though the chicks were solitarily tested in an inter-temporal choice paradigm. On the other hand, the impulsivity did not change instantaneously when the chicks were tested in competition (Amita and Matsushima, unpublished); the increase in impulsivity was observed even when there was no actual food competition, similar to our results. It remains to be determined whether the visual perception of competitive individuals directly caused the impulsivity or whether the excessive work investments secondarily caused the impulsivity. Further studies are required.

ECOLOGICAL ACCOUNTS OF SYNCHRONIZED RUNNING

The synchronized running observed in this study (Experiments 1 and 2) may be explained by "scramble kleptoparasitism" in behavioral ecology. Kleptoparasitism refers to parasitical exploitation of food that other foragers' efforts have made available (Giraldeau and Caraco, 2000). Of several variations, scramble kleptoparasitism specifically refers to the simultaneous exploitation of a sharable resource by multiple competitors with little or no aggression. This foraging behavior has also been called "social facilitation" (Curio, 1976). Barnard and Sibly (1981) regarded interactions between kleptoparasitically foraging individuals as "producer/scrounger" relationships, or a pair of alternative strategies.

It is possible that chicks running together acted as producer and scrounger, the one leading acted as a producer and the other following acted as a scrounger. In this study, we found that some individuals behaved predominantly as followers; e.g., in the bottom record of **Figure 4**, the purple-colored chick tended to follow the green-colored chick. However, the tactics were not always fixed, and chicks often changed their position in reference to the other. Foraging competition did not influence the synchrony of running (Experiment 2, **Figure 5**, bottom), indicating that chicks did scramble kleptoparasitism due to some innate or developmental factors, rather than to immediate competition over food. In accordance with this, we often observed that a chick was attracted to its pair mate and stayed at the feeder, even though the subject chick had already gained a grain at that feeder (e.g., bottom traces in **Figure 4**). To reveal the direct cause of synchronization, more elaborate analysis of running synchrony is needed.

The synchronization may also be an adaptive response to predation risk. Hamilton (1971) points out that predation could lead to the evolution of gregarious behavior by considering that predators habitually approach from outside of the herd. Furthermore, gregariousness itself "dilutes" predation risk for any particular individuals (Foster and Treherne, 1981). Highly synchronized runs observed in our study may have resulted from the gregarious instincts in chicks. It is therefore quite interesting to examine if chicks under predation pressure could run in even higher level of synchronization.

IMPLICATIONS FOR NEURAL MECHANISMS OF SOCIAL FACILITATION

In the neuroscience of decision-making, relevant brain regions and neurotransmitters/neuromodulators critical for "effort cost" (such as pressing a lever or climbing a mesh barrier to obtain food pellets) have been intensively explored (Walton et al., 2006; Floresco et al., 2008a). Several brain regions are reported to cause a work cost aversion, meaning a bias away from the costly option (e.g., climbing mesh barrier) to obtain a larger food; i.e., the anterior cingulate cortex (Rudebeck et al., 2006a), the neural pathways between the anterior cingulate cortex and amygdala, and the amygdala itself (Floresco and Ghods-Sharifi, 2007).

Systemic administration of dopamine antagonists (Denk et al., 2005; Floresco et al., 2008b) also induced the same effect. Since the anterior cingulate cortex and amygdala are thought to be involved in social behaviors (Rosvold et al., 1954; Rudebeck et al., 2006b), these regions might play a critical role in social influences of behavior by conspecifics. However, no studies have so far integrated the neuroscience of economical decision-making and the behavioral ecology of social foraging. Our next goal is therefore to clarify the neural mechanisms that underlie the social influences on work investments.

CONCLUSION

When viewed from behavioral economics and ecology, social facilitation can be characterized by increased foraging efforts and synchronization among individuals. The facilitation occurs immediately by visual perception of other individuals, rather than the accompanying food competition. The increased efforts occur not only in the approaching to food resource (running) but also in the handling food (pecking). Other factors than the gain rate should be considered, such as minimizing the starvation risk or adaptation to predation pressure.

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APPENDIX

STATISTICAL ANALYSIS USING GENERALIZED LINEAR MIXED MODEL

In Experiment 1 and 2, we focused on running distance and total time in which both chicks stayed in the same end of the maze (i.e., numerator of synchrony index) as response variables. In Experiment 3, we focused on number of pecks, number of gained grains, running distance, and velocity as response variables.

We assumed a Poisson distribution for the error structure of the data of running distance, number of pecks, and number of gained grains, considering that they were all non-negative values. $\Lambda(X)$ (>0) was thus approximated by a Poisson function (log link function) as

$$\Lambda(X) = \exp(X) \tag{1}$$

On the other hand, we assumed a binomial distribution for the error structure of the data of total time in which both chicks stayed in the same end of the maze, since the time was calculated by the number of video frames and all frames were fallen into either "same end" or "different end" category. Synchrony index = $Q(X)$ ($\in [0, 1]$) was thus approximated by a logistic function (logit link function) as

$$Q(X) = 1/(1+\exp(-X)) \tag{2}$$

in which a predictor X was linearly given as a weighed sum of explanatory variables.

Experiment 1

$$X = \beta_0 + (\beta_1 + r_{is}) * \text{day} + \beta_2 * \text{maze} + \beta_3 * \text{cage} + r_{ii} \tag{3}$$

Day (variable = 1, 2, 3, 4, or 5) denotes experimental days. Coefficient β_1 indicates how the day contributes to running distance or synchrony index. A positive value of estimated β_1 thus suggests that the running distance increases as the days elapses.

Maze (categorical variable) denotes foraging condition in the maze (i.e., single or paired). Coefficient β_2 indicates how paired foraging in the maze contributes to the response variables. A negative value of estimated β_2 suggests that single chicks in the maze ran/synchronized less than paired chicks in the maze.

Cage (categorical variable) denotes foraging condition in the cage when the main diet food was supplied (i.e., single or paired). Coefficient β_2 indicates how paired foraging in the cage contributes to the response variables. A negative value of estimated β_2 suggests that runs by single chicks in the cage ran/synchronized less than paired chicks in the cage.

Experiment 2

$$X = \gamma_0 + (\gamma_1 + r_{is}) * \text{day} + \gamma_2 * \text{maze} + \gamma_3 * \text{feeder} + r_{ii} \tag{4}$$

Maze (categorical variable) denotes the type of wall in the maze (i.e., transparent or opaque). Coefficient γ_2 indicates how visual perception contributes to the response variables. A negative value of estimated γ_2 suggests that chicks mutually invisible ran/synchronized less than chicks mutually visible.

Feeder (categorical variable) denotes whether the feeders were separated or shared. Coefficient γ_3 indicates how the actual competition over food intake contributes to the response variables. A negative value of estimated γ_3 suggests that the actual competition over food intake decreased running distance/synchrony less than chicks with no competition.

Experiment 3

$$X = \delta_0 + \delta_1 * \text{maze} + (\delta_2 + r_{is}) * \text{feeder} + \delta_3 * \text{maze} * \text{feeder} + r_{ii} \tag{5}$$

Maze (categorical variable) denotes foraging condition in the maze (i.e., single or paired).

Feeder (numeric variable; 1, 2, 3, 4, and 5) denotes difficulty of food trays. Coefficient δ_2 indicates how increasing difficulty of food trays contributes to the response variables. A positive value of estimated δ_2 suggests that the more difficult the food tray was, the larger the response variable was.

Coefficient δ_3 indicates how *maze* and feeder interact.

The intercepts (β_0, γ_0, and δ_0) denote bias at the population level. The random intercept and the random slope (against day and feeder in Experiment 1, 2, and 3, respectively) for each individual (i) was denoted by r_{ii} and r_{is}, representing noise that was not experimentally controlled; Gaussian distribution with mean = 0 was assumed.

In Experiment 1, AICs were compared among eight models with different combination of parameters; (i) *null model* (β_0), (ii) *day model* (β_0, β_1), (iii) *maze model* (β_1, β_2), (iv) *cage model* (β_1, β_3), (v) *day-maze model* (β_0, β_1, β_2), (vi) *day-cage model* (β_0, β_1, β_3), (vii) *maze-cage model* (β_0, β_2, β_3) and (viii) *day-maze-cage model* (β_0, β_1, β_2, β_3).

Similarly in Experiment 2, AICs were compared among the following eight models; (i) *null model* (γ_0), (ii) *day model* (γ_0, γ_1), (iii) *maze model* (γ_0, γ_2), (iv) *feeder model* (γ_0, γ_3), (v) *day–maze model* (γ_0, γ_1, γ_2), (vi) *day–feeder model* (γ_0, γ_1, γ_3), (vii) *maze–feeder model* (γ_0, γ_1, γ_3), and (viii) *day–maze-feeder model* (γ_0, γ_1, γ_2, γ_3).

In Experiment 3, AICs were compared among the following five models; (i) *null model* (δ_0), (ii) *maze model* (δ_0, δ_1), (iii) *feeder model* (δ_1, δ_2), (iv) *maze–feeder model* (δ_0, δ_1, δ_2), and (v) *maze–feeder-and-interaction model* (δ_0, δ_1, δ_2, δ_3).

Most likely values of the intercepts and coefficients (β_0, β_1, β_2, β_3, γ_0, γ_1, γ_2, γ_3, and δ_0, δ_1, δ_2, δ_3) were estimated on the basis of the choice data by using R (version 2.12.0; R Development Core Team, 2010) and the lme4 package (version 0.999375-37; Bates and Sarkar, 2010). AICs were given as a sum of the deviance plus two times the number of parameters. The AICs and the parameter estimates are shown in **Tables A1–A8** in Appendix for Experiment 1, 2, and 3, respectively. For interpretations of the statistic computations, see the main text.

In all tables, models are sorted in the order of AICs. Hyphen means that the model does not include the parameter. Coefficients in parentheses represents that the 95% confidence interval (CI) of the estimate included 0. CI was not considered for the intercepts (β_0, γ_0, and δ_0).

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Table A1 | The *day–maze* model yielded the smallest AIC.

	Models	AIC	Estimated coefficients of variables			
			β_0 (Intercept)	β_1 (Day)	β_2 (Maze)	β_3 (Cage)
1	[β_0, β_1, β_2]	14794	9.475460	0.033304	–0.347460	–
2	[β_0, β_1, β_2, β_3]	14794	9.442871	0.033308	–0.347421	(0.065203)
3	[β_0, β_2]	14812	9.47573	–	–0.34738	–
4	[β_0, β_2, β_3]	14813	9.44303	–	–0.34736	(0.06539)
5	[β_0, β_1]	14822	9.301773	0.033290	–	–
6	[β_0, β_1, β_3]	14823	9.269186	0.033299	–	(0.065212)
7	[β_0]	14841	9.30201	–	–	–
8	[β_0, β_3]	14842	9.26935	–	–	(0.06536)

AICs for running distance (Experiment 1). AICs and estimated coefficients of variables were calculated for 8 models designed for running distance in Experiment 1. The models are sorted in ascending order of AIC. Coefficients in parentheses represents that the 95% confidence interval (CI) of the estimate included 0. The model [β_0, β_1, β_2] indicates that both day and maze had significant effects, whereas the same-AIC. Model [β_0, β_1, β_2, β_3] indicates that cage was not reliable for its coefficient. Most-likely fitting formulas are indicated below:
Single foraging in the maze: $X = 9.128 + (0.033304 + r_{is}) \times day + r_{ii}$.
Paired foraging in the maze: $X = 9.475460 + (0.033304 + r_{is}) \times day + r_{ii}$.

Table A2 | The *day–maze* model yielded the smallest AIC.

	Models	AIC	Estimated coefficients of variables			
			β_0 (Intercept)	β_1 (Day)	β_2 (Maze)	β_3 (Cage)
1	[β_0, β_1, β_2]	4834	0.85135	–0.05698	–0.83931	–
2	[β_0, β_1, β_2, β_3]	4835	0.89544	–0.05698	–0.83924	(–0.08825)
3	[β_0, β_2]	4839	0.85106	–	–0.83970	–
4	[β_0, β_2, β_3]	4840	0.89519	–	–0.83963	(–0.08833)
5	[β_0, β_1]	4862	0.43171	–0.05700	–	–
6	[β_0, β_1, β_3]	4864	0.47585	–0.05698	–	(–0.08837)
7	[β_0]	4867	0.4311	–	–	–
8	[β_0, β_3]	4869	0.47541	–	–	(–0.08846)

AICs for synchrony index (Experiment 1). AICs and estimated coefficients of variables were calculated for 8 models designed for synchrony index (proportion of the number of video flames in which chicks were in the same end of the maze) in Experiment 1. The model [β_0, β_1, β_2] indicates that both day and maze had significant effects, whereas the second-smallest-AIC model [β_0, β_1, β_2, β_3] indicates that cage was not reliable for its coefficient.
Single foraging in the maze: $X = 0.01204 + (-0.05698 + r_{is}) \times day + r_{ii}$.
Paired foraging in the maze: $X = 0.85135 + (-0.05698 + r_{is}) \times day + r_{ii}$.

Table A3 | The *day–maze* model yielded the smallest AIC.

	Models	AIC	Estimated coefficients of variables			
			γ_0 (Intercept)	γ_1 (Day)	γ_2 (Maze)	γ_3 (Feeder)
1	$[\gamma_0, \gamma_1, \gamma_2]$	16191	9.320326	0.060972	–0.276690	–
2	$[\gamma_0, \gamma_1, \gamma_2, \gamma_3]$	16192	9.270098	0.060971	–0.226365	(0.110372)
3	$[\gamma_0, \gamma_1, \gamma_3]$	16196	9.128636	0.060968	–	0.251822
4	$[\gamma_0, \gamma_1]$	16201	9.188624	0.060951	–	–
5	$[\gamma_0, \gamma_2]$	16228	9.32036	–	–0.27610	–
6	$[\gamma_0, \gamma_2, \gamma_3]$	16229	9.27008	–	–0.22573	(0.11048)
7	$[\gamma_0, \gamma_3]$	16233	9.12902	–	–	0.25154
8	$[\gamma_0]$	16237	9.18896	–	–	–

AICs for running distance (Experiment 2). AICs and estimated coefficients of variables were calculated for 8 models designed for running distance in Experiment 2. The model $[\gamma_0, \gamma_1, \gamma_2]$ indicates that both day and maze had significant effects, whereas the second-smallest-AIC model $[\gamma_0, \gamma_1, \gamma_2, \gamma_3]$ indicates that feeder was not reliable for its coefficient.
Opaque wall: $X = 9.043636 + (0.060972 + r_{is}) \times day + r_{ii}$.
Transparent wall: $X = 9.320326 + (0.060972 + r_{is}) \times day + r_{ii}$.

Table A4 | The *day–maze* model yielded the smallest AIC, but the effect of *day* was not reliable for its coefficient.

	Models	AIC	Estimated coefficients of variables			
			γ_0 (Intercept)	γ_1 (Day)	γ_2 (Maze)	γ_3 (Feeder)
1	$[\gamma_0, \gamma_1, \gamma_2]$	14088	1.54956	(0.04025)	–1.29326	–
2	$[\gamma_0, \gamma_2]$	14089	1.5501	–	–1.2934	–
3	$[\gamma_0, \gamma_1, \gamma_2, \gamma_3]$	14089	1.42322	(0.04025)	–1.16667	(0.27757)
4	$[\gamma_0, \gamma_2, \gamma_3]$	14090	1.4236	–	–1.1667	(0.2782)
5	$[\gamma_0, \gamma_3]$	14105	0.6943	–	–	1.0073
6	$[\gamma_0, \gamma_1, \gamma_3]$	14105	0.69392	(0.04026)	–	1.00706
7	$[\gamma_0, \gamma_1]$	14110	0.93383	(0.04022)	–	–
8	$[\gamma_0]$	14111	0.9340	–	–	–

AICs for synchrony index (Experiment 2). AICs and estimated coefficients of variables were calculated for 8 models designed for synchrony index in Experiment 2. The model $[\gamma_0, \gamma_1, \gamma_2]$ indicates that day had insignificant effects.
Opaque wall: $X = 0.2567 + (0.04025 + r_{is}) \times day + r_{ii}$.
Transparent wall: $X = 1.5501 + (0.04025 + r_{is}) \times day + r_{ii}$.

Table A5 | The *maze–feeder-and-interaction* model yielded the smallest AIC.

	Models	AIC	Estimated coefficients of variables			
			δ_0 (Intercept)	δ_1 (Maze)	δ_2 (Feeder)	δ_3 (Maze:feeder)
1	$[\delta_0, \delta_1, \delta_2, \delta_3]$	434.8	2.67886	(0.04795)	0.39100	–0.07668
2	$[\delta_0, \delta_2]$	437.7	2.69015	–	0.35387	–
3	$[\delta_0, \delta_1, \delta_2]$	439.4	2.74001	(–0.09332)	0.35381	–
4	$[\delta_0]$	490.3	2.6991	–	–	–
5	$[\delta_0, \delta_1]$	492.3	2.67413	(0.04772)	–	–

AICs for the number of pecks (Experiment 3). AICs and estimated coefficients of variables were calculated for 5 models designed for number of pecks in Experiment 3. The model $[\delta_0, \delta_1, \delta_2, \delta_3]$ indicates that maze per se had no effects in the absence of feeder.
Single: $X = 2.72681 + (0.31432 + r_{is}) \times feeder + r_{ii}$.
Paired: $X = 2.67886 + (0.39100 + r_{is}) \times feeder + r_{ii}$.

Table A6 | The *feeder* model yielded the smallest AIC.

	Models	AIC	Estimated coefficients of variables			
			δ_0 (Intercept)	δ_1 (Maze)	δ_2 (Feeder)	δ_3 (Maze:feeder)
1	[δ_0, δ_2]	42.02	2.48704	–	–0.07750	
2	[δ_0, δ_1, δ_2]	44.01	2.483046	(0.007534)	–0.077502	
3	[δ_0, δ_1, δ_2, δ_3]	45.98	2.494080	(–0.013251)	–0.081384	(0.007306)
4	[δ_0]	49.77	2.26054	–	–	
5	[δ_0, δ_1]	51.76	2.25654	(0.00753)	–	

AICs for the number of gained grains (Experiment 3). AICs and estimated coefficients of variables were calculated for 5 models designed for total gain of grains in Experiment 3. The model [δ_0, δ_2] indicates that only feeder had significant effects.
$X = 2.48704 + (–0.07750 + r_{is}) \times feeder + r_{ii}$.

Table A7 | The *maze–feeder-interaction* model yielded the smallest AIC.

	Models	AIC	Estimated coefficients of variables			
			δ_0 (Intercept)	δ_1 (Maze)	δ_2 (Feeder)	δ_3 (Maze:feeder)
1	[δ_0, δ_1, δ_2, δ_3]	1640	8.41344	–0.34862	–0.07784	0.04685
2	[δ_0, δ_1, δ_2]	1643	8.41253	–0.34666	–0.05309	–
3	[δ_0, δ_2]	1650	8.22898	–	–0.05308	–
4	[δ_0, δ_1]	1655	8.41218	–0.34806	–	–
5	[δ_0]	1662	8.22792	–	–	–

AICs for running distance (Experiment 3). AICs and estimated coefficients of variables were calculated for five models designed for running distance in Experiment 3. The model [δ_0, δ_1, δ_2, δ_3] indicates that maze, feeder and their interaction had significant effects.
Single: $X = 8.06482 + (–0.03099 + r_{is}) \times feeder + r_{ii}$.
Paired: $X = 8.41344 + (–0.07784 + r_{is}) \times feeder + r_{ii}$.

Table A8 | The *maze* model yielded the smallest AIC.

	Models	AIC	Estimated coefficients of variables			
			δ_0 (Intercept)	δ_1 (Maze)	δ_2 (Feeder)	δ_3 (Maze:feeder)
1	[δ_0, δ_1]	77.45	3.65249	–0.45497	–	–
2	[δ_0, δ_1, δ_2]	77.58	3.70838	–0.45496	(–0.01875)	–
3	[δ_0, δ_1, δ_2, δ_3]	78.84	3.73782	–0.52555	(–0.02872)	(0.02379)
4	[δ_0]	93.85	3.41092	–	–	–
5	[δ_0, δ_2]	93.98	3.46683	–	(–0.01875)	–

AICs for velocity (Experiment 3). AICs and estimated coefficients of variables were calculated for 5 models designed for running velocity in Experiment 3. The model [δ_0, δ_1] indicates that only maze had significant effects.
Single: $X = 3.19752 + r_{is} \times feeder + r_{ii}$.
Paired: $X = 3.65249 + r_{is} \times feeder + r_{ii}$.

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Instantaneous and cumulative influences of competition on impulsive choices in domestic chicks

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This study examined instantaneous and cumulative effects of competitive interactions on impulsiveness in the inter-temporal choices in domestic chicks. Chicks were trained to peck colored beads to gain delayed food rewards (1 or 6 grains of millet delivered after a delay ranging between 0 and 4.5 s), and were tested in binary choices between a small–short delay option (***SS***) and a large–long delay alternative (***LL***). To examine whether competitive foraging instantaneously changes impulsiveness, we intraindividually compared choices between two consecutive tests in different contexts, one with competitors and another without. We found that (1) the number of the choice of ***LL*** was not influenced by competition in the tests, but (2) the operant peck latency was shortened by competition, suggesting a socially enhanced incentive for food. To further examine the lasting changes, two groups of chicks were consecutively trained and tested daily for 2 weeks according to a "behavioral titration" procedure, one with competitors and another without. Inter-group comparisons of the choices revealed that (3) choice impulsiveness gradually decreased along development, while (4) the chicks trained in competition maintained a higher level of impulsiveness. These results suggest that competitive foraging causes impulsive choices not by direct/contextual modification. Causal link between the instantaneous enhancement of incentive and the gradual effects on impulsiveness remains to be examined. Some (yet unspecified) factors may be indirectly involved.

Keywords: inter-temporal choices, social facilitation, social foraging, work investment, foraging effort, operant conditioning, nucleus accumbens

INTRODUCTION

Social interferences could shift behaviors that maximize the individual payoff. When an animal is foraging in competition, a food item that is spatially/temporally remote should inevitably include a higher collection risk (McNamara and Houston, 1987; Benson and Stephens, 1996), and hence decision makers may reasonably redirect their choices toward a more proximate food item even though a large alternative is available. Such a rational forager could instantaneously change its impulsiveness as soon as a potential competitor appears; otherwise, it could change its choices much more slowly and gradually after accumulating the experiences of benefits and costs.

In fact, we found, by using domestic chicks as subjects, that competitive foraging enhances impulsive choices without actual interference of individual gains (Amita et al., 2010). In inter-temporal choices between a small–short delay option (***SS***) and a large–long delay alternative (***LL***), chicks that had been trained in competition for 3 days chose the ***SS*** option significantly more frequently than those trained without competition. Chicks in both groups were tested in the same isolated condition, and the observed difference in impulsiveness was ascribed to the cumulative experiences of the perceived competition. It thus remained to be examined whether competitive foraging could cause instantaneous/contextual modification in choices and what (if any) of these modifications could underlie the observed cumulative effects.

Instantaneous effects of social facilitation have been documented in the work investments (running distance and pecking for food) in the accompanying paper by Ogura and Matsushima (2011). In the present study, on the other hand, we showed the other factors that may possibly be involved in the development of impulsiveness. First, we demonstrate that perceived competition instantaneously enhances the incentive for food, even though the choice of impulsiveness remains unchanged. The perceived competition shortened the operant peck latency, possibly as a form of social facilitation, without apparent increase in work investments. Second, we show that impulsiveness decreases by age/experience but the cumulative effects of competition are lasting, reconfirming the conclusion of our previous study (Amita et al., 2010).

MATERIALS AND METHODS

ANIMALS

A total of 24 male chicks (*Gallus domesticus*, White Leghorns) were trained, but 3 chicks were discarded because they emitted distress calls and did not eat the millet food in the operant chamber. The present study is thus based on data obtained from 21 successfully trained individuals. In addition, 18 chicks served as companion individuals, but their behaviors were not recorded. New hatchlings

(post-hatch day 1) were purchased from a local supplier, and housed in transparent plastic cages (15 cm × 28 cm × 12 cm) that were thermo-controlled at ca. 30°C under illumination (12L:12D, light period starting at 08:00). Each cage contained three chicks, all of which were trained and tested in the same conditions. On post-hatch day 2–4, each chick was fed with 1–3 g of food per day (mixture of millet and chick mash food). On day 5 and afterward, each chick received 0.5–1.0 g of millet during the experiments and was then fed once with 4 g rations in the evening. Water was freely available. After the end of the experiments, the chicks were sacrificed with carbon dioxide. Experiments were conducted under the guidelines and with the approval of the Committee on Animal Experiments of Hokkaido University. The guidelines are based on the national regulations for animal welfare in Japan (Law for the Humane Treatment and Management of Animals; after a partial amendment No. 68, 2005).

APPARATUS

We used an operant chamber for recording behaviors in the inter-temporal choice paradigm. A thermo-controlled box (21 cm × 19 cm × 25 cm, maintained at ca. 27–30°C and illuminated by light bulbs) was used (see Aoki et al., 2006). One of the surrounding walls was equipped with a pair of holes placed side by side (separated by 3 cm and placed 4 cm above floor level), through which one or two colored beads (green, blue, or red) were presented for 1 s. When a chick pecked at a bead associated with a reward, the millet food was supplied to the central food tray on the floor (placed between the two holes) after a programmed delay. Colored beads were assigned to reward options: small–short delay food (***SS*** delivered after a constant mechanical lag $\Delta = 0.29$ s in average) and large–long delay food (***LL*** delivered after *delay* $+ \Delta$). We observed the behaviors of the chicks through a video camera placed above the feeder, without being seen by the subject chicks. In experiment 1, the chamber was divided into two sections by a transparent Plexiglas partition. A subject was trained and tested in one section, and a pair of free-riding companion chicks received food in the opposite section (**Figure 1A**). Each section was equipped with a feeder, and the two feeders were separated by 3 cm. The chicks could see each other through the Plexiglas partition; the beads and food trays were also visible. As described previously (Amita et al., 2010), the fictitious social foraging that is not accompanied by actual interference of individual gain is referred to as "perceived competition."

PROCEDURES

Experiment 1

A blue bead was associated with a large–long delay reward (***LL***, 2 grains delivered after a long delay = 1.5 s + Δ), and a red bead was associated with a small–short delay alternative (***SS***, 1/3 grain after Δ). A green bead was non-rewarding (***S***−). Chicks were trained in two blocks (a no-competition and a competition block) per day for three successive days (post-hatch day 7–9), and subsequently tested in two blocks (a no-competition and a competition block) on day 10 (**Figure 1A**). The order of the no-competition and the competition blocks was randomized in both training and test. The training block consisted of 48 pseudo-randomly arranged trials: 12 trials with ***LL***/***S***−, 12 trials with ***SS***/***S***−, and 24 trials with ***S***−/***S***−.

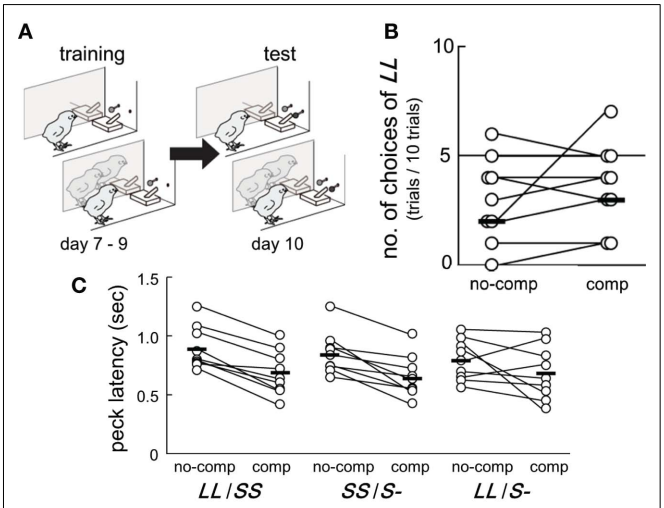

FIGURE 1 | Competition in the test did not instantaneously change inter-temporal choices but shortened the operant peck latency. Data obtained from a group of chicks ($n = 9$) are shown. **(A)** Experimental procedure of training (post-hatch day 7–9) and test (day 10). In both blocks, the subject chick was separated from two other accompanying chicks by a transparent Plexiglas partition. **(B)** Numbers of choices of ***LL*** (out of 10 test trials in total) were recorded in the no-competition and the competition blocks. The order of these two test blocks was counterbalanced. Connected pairs of circles denote individuals, and short horizontal bars indicate the median in the group. **(C)** Latency of the first operant peck at the colored bead was shorter in the competition block than in the no-competition block.

The test block consisted of 60 pseudo-randomly arranged trials: 10 trials with ***LL***/***SS***, 10 trials with ***LL***/***S***−, 10 trials with ***SS***/***S***−, and 30 trials with ***S***−/***S***−. Inter-trial intervals varied between 15 and 20 s. ITIs were not adjusted according to the trial types. In order to mimic the variation in the food gain in the group of three chicks, we assumed that each chick had an equal chance to get each grain in the competition and set the amount to vary at every trial according to a binomial distribution (see Amita et al., 2010). For ***SS***, 1 grain was supplied in 24 trials and no food was supplied in the remaining 48 trials so that the mean was 1/3 grain per trial for 72 trials (0 grain in 48 trials and 1 grain in 24 trials; pseudo-randomly arranged sequence). Similarly, for ***LL***, 0–6 grains were supplied and the mean amount was set at 2 grains per trial for 72 trials (0 grain in 11 trials, 1 grain in 12 trials, 2 grains in 26 trials, 3 grains in 16 trials, 4 grains in 4 trials, 5 grains in 2 trials and 6 grains in 1 trial; pseudo-randomly arranged sequence). On day 10 (test), 1 and 6 grains were given for ***SS*** and ***LL***, respectively. The pair of companion chicks was given 3 grains at the time when the subject gained food.

Experiment 2

A blue bead was associated with a large–long delay reward (***LL***, 6 grains delivered after a long delay), and a red bead was associated with a small–short delay alternative (***SS***, 1 grain after a delay of Δ). A green bead was non-rewarding (***S***−). Chicks were trained for 12 days, from post-hatch day 7 to 19 (except day 13), either in isolation (no-competition) or in a group of 3 individuals (competition; **Figure 2A**). Note that experiment 2 is a between-subject

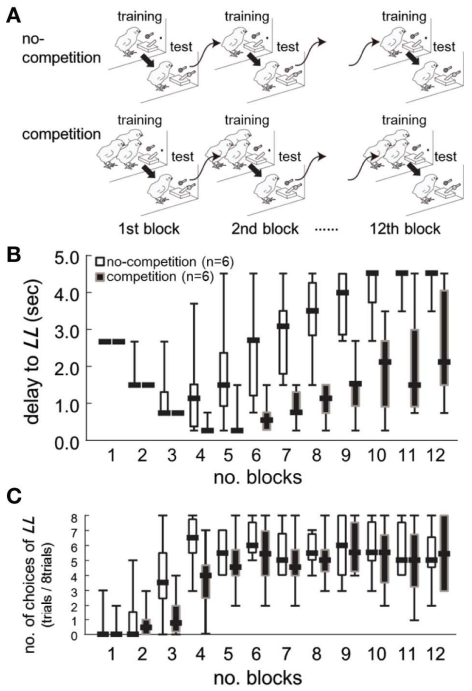

FIGURE 2 | Competition caused lasting and cumulative effects on impulsiveness. Data obtained from the two groups of chicks ($n = 6$ each) are shown. **(A)** Experimental procedure of the behavioral titration. By adjusting the delay to the large–long delay reward [***LL***, **(B)**], we searched for an equilibrium point at which both options were equally chosen **(C)**. Chicks were trained and tested for 12 days (1 block per day) from post-hatch day 7. In the no-competition group (upper), chicks were trained in isolation. In the competition group (lower), chicks were trained in a group of three chicks. Note that chicks were tested in isolation in both groups. **(B)** Delay to ***LL*** was plotted against the number of blocks. Short horizontal bars indicate the median, boxes the 25–75% range, and whiskers the min–max range, respectively. **(C)** The number of choices of ***LL*** was similarly plotted.

design. In competition, two chicks served as companion individuals. The partitioning Plexiglas was not used in experiment 2. It is noteworthy that the food was shared among individuals and the chick that pecked the bead did not necessarily gain all of the grain. Though we did not record the amount of food that each individual gained, we assumed that a longer delay to ***LL*** did not lead to a higher probability of interception of the food by the companion individuals, because the interception occurred after the end of the delay period.

It might be argued that the competitor chicks interfere with the subject in learning in forming the association between the colored beads with rewards. The chicks in competition could learn the association more slowly than those in no-competition due to the distractive effects of competitors. In this study, in order to avoid the possible interference of learning, we gave pre-training blocks before the behavioral titration started (see below for details). We also accomplished a supplementary experiment (see **Figure A2** in Appendix) in order to directly examine the effects of interference.

Before the titration procedure started, in order to make subject chicks to form the associations between the colored bead and the rewards, the chicks received two blocks of pre-training, one per day (day 5–6), either in isolation (no-competition) or in a group of three individuals (competition). One bead was presented per trial (namely, forced choice trials), and no binary choice trials were given in the pre-training. In pre-training blocks, the delay to ***LL*** was set at 0.29 s. If the chicks pecked a green bead (***S***−), the bead was repeatedly presented (up to five trials) until chick stayed not to peck the bead (correction trials). The pre-training block consisted of 72 pseudo-randomly arranged trials: 18 trials with ***LL***, 18 trials with ***SS*** and 36 trials with ***S***−. The chicks received one block of training and one block of testing each day. The same chicks were used across test blocks. The training block consisted of 72 pseudo-randomly arranged trials: 18 trials with ***LL***/***S***−, 18 trials with ***SS***/***S***−, and 36 trials with ***S***−/***S***−. The test block consisted of 48 pseudo-randomly arranged trials: 8 trials with ***LL***/***SS***, 8 trials with ***LL***/***S***−, 8 trials with ***SS***/***S***−, and 24 trials with ***S***−/***S***−. Inter-trial intervals varied between 15 and 20 s. For behavioral titration, we adopted a procedure similar to that employed by Kawamori and Matsushima (2010). Briefly, the delay to ***LL*** was incremented (or decremented) in the nth training and testing block if the chick chose ***LL*** for more than 5 (or less than 3) out of the 8 ***LL***/***SS*** test trials in the preceding $(n-1)$th block. The delay to ***LL*** was unchanged in the nth block if the chick chose ***LL*** for 3–5 trials out of the 8 test trials in the $(n-1)$th block. The choice ratio was adjusted by changing the ***LL*** delay in six steps (0.29, 0.75, 1.50, 2.66, 3.48, and 4.51 s, including the mechanical lag $\Delta = 0.29$ s).

We daily measured the subjects' body weight during behavioral titration but detected no differences between the groups (see **Figure A3** and **Table A5** in Appendix).

STATISTICAL ANALYSIS

We analyzed data by using R (computer language developed for statistical computations, version 2.6.0). Generalized linear mixed models (GLMMs) were constructed to fit the observed data: the number of choices and the peck latency in experiment 1 (**Tables A1** and **A2** in Appendix), and the delay to ***LL*** in experiment 2 (**Table A4** in Appendix). For the number of choices in the test phase of experiment 2, multiple comparisons by a binomial test were used after sequential Bonferroni corrections (**Table A3** in Appendix).

RESULTS

EXPERIMENT 1

Perceived competition did not cause any instantaneous changes in inter-temporal choices, but clearly shortened the operant peck latency at test (day 10). Results showed that six out of nine chicks chose ***LL*** less frequently than ***SS*** in both the no-competition and the competition blocks (**Figure 1B**). The numbers of choices of ***LL*** were fitted by GLMM (**Table A1** in Appendix) by including *competition* (no-competition or competition block) and *order* (whether the competition block preceded or followed by the no-competition block) as explanatory variables. Model selection by Akaike information criteria (AIC) showed that the null model yielded a smaller AIC (=30.74) than the *competition* model (31.76), the *order* model (32.74), and the *competition* + *order* model (33.76). Therefore, we are unable to conclude that perceived competition instantaneously changes the choices.

In all nine chicks, peck latency was shorter in the competition block than in the no-competition block in both the ***LL***/***SS*** and the ***SS***/***S***− trials (**Figure 1C**). Similarly, in the ***LL***/***S***− trials, seven of nine chicks showed shorter peck latency in the competition block. Peck latencies were fitted by GLMM (**Table A2** in Appendix) by including *competition*, *trial types* (***SS***/***S***− or ***LL***/***S***− and interactions between *competition* and *trial types* as explanatory variables. The model composed only of *competition* yielded the smallest AIC (=88.53), suggesting that competition shortened the peck latency irrespective of the trial types. However, in model 2, which had the second smallest AIC (=95.76), the estimated coefficient of the *trial types* was positive, suggesting that the latency might be longer in the ***SS***/***S***− trials than the ***LL***/***S***− trials, somehow incompatible with the choice data (**Figure 1B**; see Discussion below). Furthermore, in model 3, which had a larger AIC, the estimated coefficient of the interaction term (between *competition* and *trial types*) was negative, suggesting that the effect of competition might be larger in the ***SS/S***− trials than in the ***LL/S***− trials. We compared these four models (including the null model) by likelihood-ratio test, and found no significant differences between model 1 and 2 ($p = 0.79$) and also between model 1 and 3 ($p = 0.34$), but difference was significant between model 1 and 4 ($p < 0.01$). We therefore conclude that *competition* primarily contributed to the shortening latency.

EXPERIMENT 2

Competition caused lasting and cumulative effects on impulsiveness. The delay to ***LL*** (**Figure 2B**) served as a measure of the impulsiveness when the choices of ***LL*** (**Figure 2C**) were balanced in the titration procedure. We compared the choice data in each block by using a binomial test (**Table A3** in Appendix), but the difference between the groups was significant only in the fourth block (sequential Bonferroni correction for multiple comparisons, Hommel, 1988; $p < 0.05$). We therefore fitted the delay to ***LL*** data from the 5th to 12th blocks by GLMM (**Table A4** in Appendix) by including *competition* (no-competition or competition) and *block* (the number of the block) as explanatory variables (**Table A4** in Appendix). The *competition* + *block* model yielded the smallest AIC (=42.74), whereas the *block* model (52.48) and the *competition* model (60.94) yielded larger AICs. The estimated coefficient of the *block* term was positive, indicating that in both groups, the impulsiveness decreased as the chicks grew. On the other hand, the estimated coefficient of the *competition* term was negative, indicating that *competition* caused a lasting facilitation on impulsiveness.

Competition may have interfered with the association between cues and rewards. In experiment 2, slower shift for ***LL*** in the competition group may be explained by a slower learning because competitors could serve as distractors, which interfered with the associative learning. However, the chicks in both groups always chose ***S***+ beads in the ***S***+/***S***− trials in the test blocks (**Figure A1** in Appendix); the percentage of correct responses (no peck) did not differ also in the ***S***−/***S***− trials. We therefore conclude that the effects of competition on impulsiveness cannot be ascribed to the interference in learning. Further direct examination (**Figure A2** in Appendix) failed to reveal the possible interference by competition. If competition interfered with associative learning, the chicks would choose more frequently the colored bead learned in no-competition than that in competition. However, biased choices were not found between such color cues.

DISCUSSION

Perceived competition shortened the peck latency, but it failed to change instantaneously the impulsive choices (experiment 1). If the shorter response latency represented a more valuable option, as has been argued (Brown and Bowman, 1995; Lauwereyns and Wisnewski, 2006), the present results suggest that perceived competition enhances the chicks' incentive for food. The peck latency in the ***SS***/***S***− trials were, however, even longer than the ***LL***/***S***− trials (**Figure 1C**), whereas the choices were biased in favor of the ***SS*** (**Figure 1B**). It should be noted that the chicks always pecked the rewarding bead when the alternative was ***S***− (see **Figure A1** in Appendix). We also found no significant correlation between the number of choice of ***LL*** and the peck latencies at the individual level (data not shown). Therefore, shorter peck latency did not necessarily represent a more valuable option in this study using chicks.

It is possible that foraging incentive could have a direct control on the impulsiveness. It has been reported that a decrease in water deprivation level causes an increase in response latency in rats (Richards et al., 1997); they further examined the effects of the deprivation on impulsiveness, but found no effects. In our present study (experiment 1), similarly, perceived competition shorted the peck latency, but did not enhance the impulsiveness. We therefore argue that the incentive does not have a direct and strong link to the impulsive choices.

When viewed ecologically, the shortened peck latency could be an adaptive trait. For foragers that forage in kleptoparasitism, as do chicks, both forms of impulsiveness (in the pecking action and the choice of ***SS***) might be adaptive traits. Particularly, in the framework of scramble kleptoparasitism, several individuals simultaneously exploit a food resource with little or no aggression and the players' payoff is assumed by the producer–scrounger game (Giraldeau and Caraco, 2000). Producers search their environment for food clumps, and scroungers attend to other foragers' discoveries and scrounge. The critical point is that the payoff depends on the proximity; the producer gains more from a more proximate food resource, and the scroungers gain more from more proximate producers (Di Bitetti and Janson, 2001). The shortened peck latency (experiment 1) and impulsive choices (experiment 2) could efficiently increase the forager's gain, in both the producer and the scrounger.

In the experimental situation adopted in this study, however, the impulsive choice did not contribute to a higher gain. The total amount of food decreased when chicks made more impulsive choices. Similarly, the shortened peck latency did not lead to a greater payoff, because the food amount remained unchanged irrespective of whether the chick rushed or not. These results suggest that the behaviors of chicks are predisposed and not dependent on the actual benefit that the subjects gain. Ecological accounts are also useful in this context. For foragers that find and eat tiny food particles, such as star-nosed mole rats, short handling time has a marked effect on profitability (energy gained per handling time; Catania and Remple, 2005). In chicks, similarly, even a slight shortening in the peck latency by a few tenths of a second could significantly increase the food profitability in the natural context of competitive foraging.

It remains to be elucidated how impulsiveness cumulatively changes after competitive experiences. As shown in the accompanying paper by Ogura and Matsushima (2011), the perception

of other individuals is also effective in instantaneously increasing the work investments/foraging efforts. A similar competition, however, fails to cause an immediate change in impulsiveness, as revealed in this study. The shortened peck latency might be assumed as a form of social facilitation, as has been widely reported in psychology (Matlin and Zajonc, 1968). However, apparent increase in running distance and number of pecks were not found in this study. It is interesting to study whether the social facilitation without work investments/foraging efforts could cause the cumulative development of impulsiveness, and if so, which of the facilitated behaviors could be specifically responsible.

It is an open question as to whether the social facilitation and the impulsiveness have common or distinct neural mechanisms. Lesions of nucleus accumbens (NAc) induce impulsive choices in rats (Cardinal et al., 2001) and also in chicks (Izawa et al., 2003). Neurophysiological characterization of their NAc and the surrounding areas in the ventral striatum has revealed a population of neurons that selectively code the proximity and amount of anticipated food reward (Yanagihara et al., 2001; Izawa et al., 2005). A recent study in rats has also revealed that neurons in the ventral striatum represent the delay and the size of the food reward, and the firing rate was negatively correlated with the response latency (Roesch et al., 2009). It is plausible that the neural codes of reward anticipation in the ventral striatum could become modified after competition.

The neuromodulatory action of dopamine may accompany the instantaneous effects on the peck latency and the work investment. It is reported that low-cost cues produce a significantly larger increase in NAc dopamine concentration than do high-cost cues. Moreover, immediate reward cues in the delay task evoke a larger dopamine increase than do delayed reward cues (Day et al., 2010). On the other hand, experimental depletion of dopamine in the caudate nucleus increases response latency (Amalric and Koob, 1987). It is therefore possible that the enhanced release/action of dopamine in NAc could lead to the instantaneous effects of competition. Causal links between the instantaneous and the cumulative effects of competition need further experimental study.

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APPENDIX

We focused on the number of choices of ***LL*** as the response variable. Since chicks were tested in binary choices, we assumed a binominal distribution for the error structure of the data of choice ratio, and the choice probability = ***Q(X)*** ($\in[0, 1]$) was approximated by logit link function such as,

$$\boldsymbol{Q(X)} = 1/(1 + \exp(-\boldsymbol{X})) \tag{A1}$$

in which a predictor X was linearly given as a weighed sum of explanatory variables.

$$X = \beta_0 + \beta_1 * \text{competition} + \beta_2 * \text{order} + r_i \tag{A2}$$

The competition denotes a category type variable: 0 for no-competition and 1 for competition, respectively, and the order (variable = 1, 2) denotes whether the test in competitive context was accomplished before (order = 1) or after (order = 2) the test in non-competitive context; r_i denotes the individual difference. Note that the model 1 included only the intercept and individual random difference. In the model 2 with a slightly larger AIC value, however, the 95% confidence range of the β_1 involved 0, indicating that the competition did not account for the choice.

Trials in ***SS***/***S***− and ***LL***/***S***− trials were included, but the data in ***SS***/***LL*** trials were omitted. We assumed a Poisson distribution for the error structure of the data of the peck latency considering that they were all non-negative values. $\boldsymbol{\Lambda}(\boldsymbol{X})$ (>0) was thus approximated by a Poisson function (log-link function) as,

$$\boldsymbol{\Lambda}(\boldsymbol{X}) = \exp(\boldsymbol{X}) \tag{A3}$$

in which a predictor X was linearly given as a weighed sum of explanatory variables.

$$X = \beta_0 + \beta_1 * \text{competition} + \beta_2 * \text{trail types} + \beta_3 * \text{competition:trail types} + r_i \tag{A4}$$

The competition denotes a category type variable: 0 for no-competition and 1 for competition, respectively. The trial types denotes a category type variable: 0 for ***LL***/***S***− and 1 for ***SS***/***S***−. r_i denotes the individual difference.

Estimated coefficients β_1 of the effects of competition in the models 1 to 3 suggest that the chicks shortened the peck latency in competitive block, irrespectively of the trial types. The model 1 that took only competition into account was chosen with the smallest AIC value. On the other hand, the model 2 suggests a positive β_2 coefficient for trial types, suggesting latency was slightly longer in the ***SS***/***S***− trials than ***LL***/***S***− trials. Similar tendency was detected in the model 3, in which β_3 (for interaction between competition and trial type) was negative, suggesting that the competition effect was larger in the ***SS***/***S***− trials than ***LL***/***S***− trials.

Between the two groups of chicks (no-competition vs. competition), statistically significant differences were found only on day 4, in which the calculated p-value was smaller than $\pi/(n - i + 1)$. Here, the blocks were rearranged in the order of the p-value; n denotes the total number of blocks (12), and i the block number (1–12), respectively. The experiment-wide level of significance was set at $\pi = 0.05$.

The model that took both competition and block number into account was chosen with the smallest AIC value. In constructing the model, we focused on the delay to ***LL*** as the response variable. Since the delays were non-negative discrete values, we assumed a Poisson distribution for the error structure of the data. A delay to ***LL*** = ***Q***(***X***) (>0) was thus approximated via log-link function as

$$\boldsymbol{Q(X)} = \exp\boldsymbol{(X)} \tag{A5}$$

in which the linear predictor ***X*** was given as a weighed sum of explanatory variables.

$$\boldsymbol{X} = \beta_0 + \beta_1 * \text{competition} + \beta_2 * \text{block} + r_i \tag{A6}$$

The competition denotes a category type variable: 0 for no-competition and 1 for competition, and the block denotes a variable (=5–12), respectively. Coefficient β_1 indicates how the competition contributed, and β_2 indicates how the number of blocks contributed to the delay to ***LL***; r_i denotes the individual difference. Asterisks indicate that the 95% confidence range of the estimated coefficient did not involve 0. The model 1 with model 2 were further compared by likelihood-ratio test, giving rise to a significant difference ($p = 0.0006115$).

Table A1 | Numbers of choices of LL (data shown in Figure 1B) were analyzed by GLMM, and the null model that was composed of intercept (β_0) and individual random difference (r_i) was chosen.

Models	AIC	Estimated coefficients of variables		
		β_0 (intercept)	β_1 (competition)	β_2 (order)
1 (β_0)	30.74	−0.7647*	–	–
2 (β_0, β_1)	31.76	−0.9323*	0.3256	–
3 (β_0, β_2)	32.74	−0.7646	–	−0.00001
4 (β_0, β_1, β_2)	33.76	−0.8888	0.3284	−0.0299

Table A2 | Peck latency (data shown in Figure 1C) was analyzed by generalized linear mixed model (GLMM) with log-link function.

Models	AIC	Estimated coefficients of variables			
		β_0 (intercept)	β_1 (competition)	β_2 (trial types)	β_3 (competition:trial types)
1 (β_0, β_1)	88.53	0.81505	−0.14919	–	–
2 (β_0, β_1, β_2)	95.76	0.81146	−0.14924	0.04902	–
3 (β_0, β_1, β_2, β_3)	99.62	0.79102	−0.14924	0.00732	−0.08094
4 (β_0)	108.1	0.73818	–	–	–
5 (β_0, β_2)	115.3	0.73509	–	0.00624	–

Table A3 | Numbers of choices of *LL* along the 12 test blocks (data shown in Figure 2C) were analyzed by multiple comparisons after sequential Bonferroni corrections (Hommel, 1988).

No. block	4	3	6	10	5	7	8	2	11	12	1	9
p-Value	0.0033	0.0049	0.2508	0.5089	0.5220	0.5220	0.6624	0.7576	0.8183	0.8286	1.0000	1.0000
$\pi/(n-i+1)$	0.0042	0.0045	0.0050	0.0056	0.0063	0.0071	0.0083	0.0100	0.0125	0.0167	0.0250	0.0500

Table A4 | Delay to *LL* (data shown in Figure 2B) was analyzed by generalized linear mixed model (GLMM).

Models	AIC	Estimated coefficients of variables		
		β_0 (intercept)	β_1 (competition)	β_2 (block)
1 (β_0, β_1, β_2)	42.74	0.6370*	−0.6118*	0.1051*
2 (β_0, β_2)	52.48	0.3278	–	0.1051*
3 (β_0, β_1)	60.94	1.5588*	−0.6119*	–
4 (β_0)	70.69	1.2496*	–	–

Table A5 | Daily recorded body weight (data shown in Figure A3) was analyzed by generalized linear mixed model (GLMM) with a linear function. The models 1 and 2 yielded similar AIC values, but a comparison by likelihood-ratio test revealed no significant difference between the two models ($p = 0.4492$), suggesting that the competition did not influence the growth.

Models	AIC	Estimated coefficients of variables		
		β_0 (intercept)	β_1 (competition)	β_2 (block)
1 (β_0, β_1, β_2)	694.7	40.5928	0.7083	1.8768
2 (β_0, β_2)	694.9	40.9470	–	1.8768
3 (β_0, β_1)	975.6	52.7917	0.7083	–
4 (β_0)	976.2	53.1458	–	–

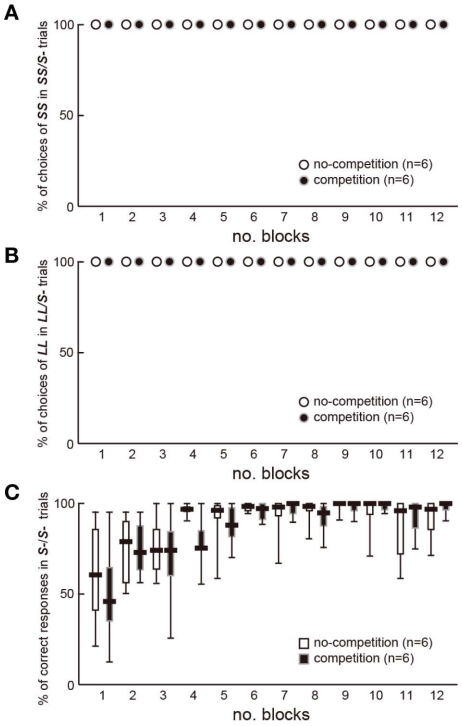

FIGURE A1 | No difference was found in their learning profiles between the two groups of chicks in experiment 2 (*n* = 6 each). **(A)** Percentage of choices of ***SS*** in 8 ***SS***/***S***– trials in each test block was plotted against the number of block. **(B)** Percentage of choices of ***LL*** in 8 ***LL***/***S***– trials in each test block was plotted against the number of block. **(C)** Percentage of correct responses (no peck) to ***S***– in 24 ***S***–***S***– trials in each test block was plotted against the number of block. Short horizontal bars indicate the median, boxes 25–75% range, and whiskers min–max range, respectively. GLMM analysis of the % correct responses in ***S***–/***S***– trials revealed that the model with the smallest AIC included only the number of blocks as explanatory variable.

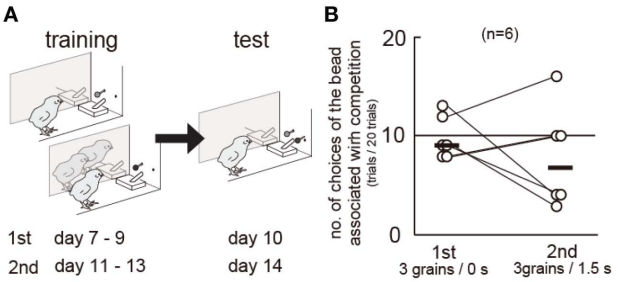

FIGURE A2 | Biased choices were not found between the colored bead associated with competition and that with no-competition. Data obtained from a group of chicks ($n = 6$) are shown. **(A)** Experimental procedure of training and test. The subject chick was separated from the accompanying chicks by a transparent Plexiglas, so that actual interference of food reward did not occur. In the first set of blocks, a blue (or green) bead was associated with competition and 3 grains after $\Delta = 0$ s, and a green (or blue) bead was associated with no-competition and 3 grains after $\Delta = 0$ s. We had confirmed that chicks distinguished these two colors in experiment 1. Chicks learned this association from day 7 to day 9, and were tested between two colors (day 10). In the second set of blocks, similarly, colored beads were associated with food both after $\Delta = 1.5$ s. Chicks relearned from day 11 to day 13), and were tested (day 14). The color assignment counterbalanced in the group ($n = 3$ for each). **(B)** Numbers of choices of the colored bead associated with competition were recorded in the first and the second sets. Connected pair of circles denote each individual chick, and short horizontal bars indicate the median of the group.

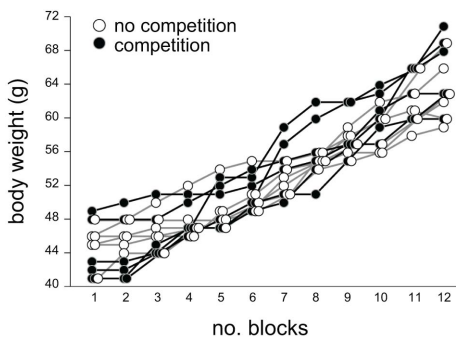

FIGURE A3 | Body weight of individuals in the two groups of chicks in experiment 2 (Figure 2) was plotted against number of blocks. Chicks of both groups similarly grew irrespectively of the training contexts.

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Coding of reward probability and risk by single neurons in animals

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Probability and risk are important factors for value-based decision making and optimal foraging. In order to survive in an unpredictable world, organisms must be able to assess the probability and risk attached to future events and use this information to generate adaptive behavior. Recent studies in non-human primates and rats have shown that both probability and risk are processed in a distributed fashion throughout the brain at the level of single neurons. Reward probability has mainly been shown to be coded by phasic increases and decreases in firing rates in neurons in the basal ganglia, midbrain, parietal, and frontal cortex. Reward variance is represented in orbitofrontal and posterior cingulate cortex and through a sustained response of dopaminergic midbrain neurons.

Keywords: uncertainty, dopamine, basal ganglia, orbitofrontal cortex, neuroeconomics

Animals in the wild must interact with the environment and harvest primary rewards such as food and reproductive opportunities to maximize the likelihood that their genetic information survives in future generations. Outside the controlled conditions of the laboratory the time and place that these positive events occur can often not be predicted with total accuracy. In order to survive in such an unpredictable and risky world, organisms must be able to assess not only the probabilities attached to future rewards but also the precision of these estimates and use this information to behave appropriately. Behavioral ecologists have studied the effects of uncertainty on foraging in animals for many decades, but only in recent years have we begun to understand how it is coded in the brain and how this information relates to choice.

Before describing their neuronal correlates, we consider briefly the definition of unpredictability and risk and the methodological issues arising from studying them in humans and animals. In the lay concept, risk increases with the perceived chance that a bad outcome (i.e., an event that yields negative subjective value) will occur. In the context of animals living in the wild, this typically translates as the probability of death, either through predation or starvation. However, because these long term hazards carry such extreme negative values it is difficult to examine them quantitatively in the laboratory on a trial-by-trial basis (Real and Caraco, 1986). As a result, the majority of studies at both the behavioral and neural levels have defined uncertainty according to economic and mathematic principles, allowing researchers to define uncertainty at discrete points in time and to study the effects of these parameters on individual decisions. In contrast to the traditional and lay usage of uncertainty, these principles have provided a more precise and quantitative approach.

Economists and decision theorists interested in human behavior typically divide uncertainty into two distinct concepts; risk, where the probabilities of potential outcomes are known and ambiguity, where the probabilities are not precisely known (Knight, 1921; Ellsberg, 1961; "uncertainty" and "ambiguity" are sometimes also used synonymously). However, other forms and conceptualizations of unpredictability are conceivable and the question whether humans outside the lab sharply distinguish between risk and ambiguity could be investigated further. In human terms, a risky decision might be to gamble on the outcome of a fair roulette wheel, whereas an ambiguous decision might be to gamble on the outcome of a football game. Formally, risk can be defined according to the statistical properties of outcome distributions, such as dispersion (i.e., variance or the related SD or coefficient of variation), skewness, or kurtosis (**Figure 1**; Burke and Tobler, 2011). These objective statistical properties are not precisely known for an ambiguous option, thereby again providing, at least conceptually, a sharp distinction between risk and ambiguity.

Real and Caraco (1986) identify two problems that all organisms must overcome in a stochastic environment in order to generate adaptive behavior. Firstly, an organism must learn and keep in mind the outcome probability distributions attached to certain actions and then select a strategy for exploiting these distributions to maximize fitness. The goal of neuroscientific research on decision making under uncertainty has been to discover how the brain solves these two problems by coding the parameters and translating this information into actions. The vast majority of such research has been performed using human subjects, primarily in conjunction with functional magnetic resonance imaging (fMRI). This has increased our understanding of the anatomical substrates of reward uncertainty processing to a large degree and has also revealed interesting parallels between sensorimotor and economic decision processes (Braun et al., 2011; Wu et al., 2011). Yet, the low spatial and temporal resolution of fMRI data does not allow researchers to see the fast signaling of reward information

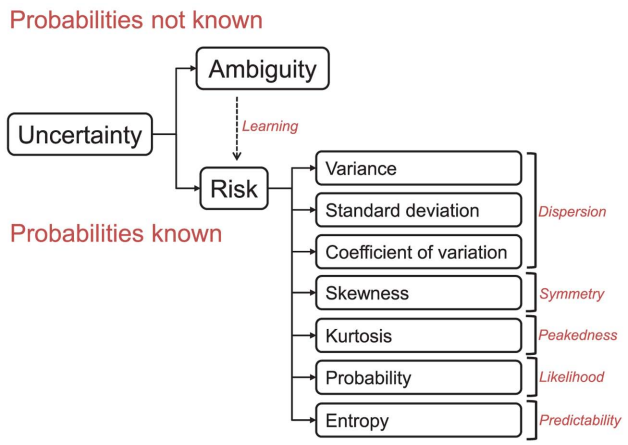

FIGURE 1 | Different forms of reward-related uncertainty. Ambiguity arises when the probabilities associated with a reward distribution are not fully known. When probabilities are known, then the situation is risky. The definition of risk used in the described studies is distinct from that used in everyday language (for example, risky prospect is one where the probability of a loss is non-zero). Instead, risk is defined by a number of parameters that describe the properties of the underlying reward distribution. Careful task design can allow researchers to disentangle neuronal responses to different forms of uncertainty through the independent manipulation of these parameters. For example, to show that a neuron responds to variance, it is necessary to hold probability constant and also check that this response does not vary with magnitude (O'Neill and Schultz, 2010). Risk and ambiguity can also be separated through stimulus design (Hayden et al., 2011). Note that entropy, SD, variance, and coefficient of variation correlate with each other (but not monotonically with probability). Their separation is therefore more difficult to achieve through task design and might be particularly sensitive to noise in the data.

by individual neurons. fMRI is also not suited to observing the large degrees of heterogeneity in both response properties and task-related activity of single neurons within small regions of interest. In order to elucidate the temporal propagation of reward uncertainty signals in subcortical and cortical regions, single cell recordings must be made in animals, typically in behaving rats and monkeys.

However, using animals in research on the neural mechanisms of decision making under risk poses a different set of challenges from those in human studies. One such issue is whether the economic definitions of risk, envisaged to provide normative or descriptive explanations of human behavior, apply to animal behavior at all. Indeed, the ability of humans to process uncertainty and exploit the information to succeed in the environment may represent a recent evolutionary addition to our cognitive skills that may not be possessed by animals at all. For example, for foraging animals in the wild, the sharp distinction between risk and ambiguity may not be so clear. Animals have to infer the properties of outcome distributions through repeated sampling and learning, thereby gradually turning ambiguity into risk (a similar process may also occur in more controlled lab conditions; Rosati and Hare, 2011). Moreover, mathematical abilities and the use of numerical representations are more limited in animals compared to humans. For these reasons, the cognitive tasks used to probe behavioral and neural responses to uncertainty in animals differ from those used in human experiments and are typically based on paradigms previously used in animal learning theory. In the present paper we separately review the forms of uncertainty that have been tested experimentally in animals and describe the neurophysiological data relating to each type.

The experiments discussed in this review all use single or multiple microelectrodes to record the extracellular potential changes from cell bodies in the immediate vicinity of the electrode tip. In a similar manner to the normative delineations between different types of uncertainty, the descriptive neurophysiological results can be crudely separated into two groups. The majority of animal experiments on reward uncertainty signals have manipulated reward probability in an effort to elucidate the neural mechanisms of learning or value processing. By contrast, only a small number of studies have been conducted with a specific emphasis on economic risk or reward variance and these have focused primarily on cortical areas.

PROBABILITY IN PARIETAL AND FRONTAL CORTEX

A simple way to manipulate reward uncertainty is to change the probability with which reward occurs following a cue or an action. Behavioralists have long known that animal decisions are based on reward probability in addition to reward magnitude (Herrnstein and Vaughn, 1980), with the assumed goal of maximizing the reward rate (Stephens and Krebs, 1986). Although a number of studies had previously investigated neural responses to reward expectation (Watanabe, 1996; Schultz et al., 1997), the first experiment to record probability-related activity of single neurons from an economic point of view was probably conducted by Platt and *Glimcher* (1999). Motivated by previous research implicating the lateral intraparietal (LIP) area as an interface between sensory- and action-related neural information in the brain (Goldberg et al., 1990; Snyder et al., 1997), they hypothesized economically relevant aspects of the decision environments might be represented there for translation into action. Indeed, LIP neurons were sensitive to expected reward magnitudes, but also modulated their firing rates in response to the probability that a specific rewarded action would be instructed (Platt and *Glimcher*, 1999).

This work laid the foundations for Sugrue et al. (2004) to record from LIP neurons during a harvesting task in which the reward probability of an unchosen option increased with the number of times it had not been chosen. In this task the optimal behavior is to distribute choices for each option according to the relative probabilities that each option would be rewarded. The monkeys were able to perform this task exceptionally well, with similar behavior to computer simulations using an optimal strategy. The activity of LIP neurons correlated with the relative values of targets in the response field of the cells, and this value was related to the probability that a saccade to each target would result in a reward. These recordings robustly support the idea that the brain computes reward probability, although it remains unclear if LIP neurons code probabilities in a pure fashion, separately from other reward-related, sensory, or behavioral information. Other parts of parietal cortex, such as the parietal reach region (PRR) code reward probability between the sensory and motor phases of a memory-guided reaching task. More specifically, the activity of PRR neurons

correlated with differential reward probability information during a memory period (1.2–1.8 s) after a cue, the size of which predicted reward with high ($p = 0.8$) or low ($p = 0.4$) probability (Musallam et al., 2004). Due to the suspected role of parietal cortex in integrating sensory and action information it is possible that these signals represent late and multiplexed information relevant to the decision process, with afferent or further upstream cells coding more basic reward information, such as probability.

Many neurons in the orbitofrontal cortex (OFC) appear to code reward probability independent of other task-relevant information such as future action, sensory information, or other reward-related parameters. The OFC is innervated by dopaminergic neurons originating in the ventral tegmental area via the mesocortical pathway, and has strong reciprocal connections with other subcortical reward-related regions such as the amygdala and striatum (Barbas and De Olmos, 1990; Cavada et al., 2000). van Duuren et al. (2009) investigated rat OFC responses by pairing different odors with 0, 50, 75, and 100% chance of receiving a rewarding outcome (a food pellet). During the course of one trial, rats were trained to sample an odor for 1.5 s, then proceed to a reward delivery port where they waited for 1.5 s until the outcome was delivered. A number of neurons coded the probability of the reward during the waiting phase (before food was delivered) with increasing or decreasing firing rates. A small number of neurons were found to respond to reward probability in this manner during the movement from odor sampling to reward delivery ports and also after the reward was delivered.

The result that small numbers of OFC neurons code reward probability in a pure manner is also supported by the work of Kennerley et al. (2009), who recorded simultaneously from OFC, anterior cingulate cortex (ACC), and lateral prefrontal cortex (LPFC) of monkeys. In their task, monkeys were trained to choose between abstract stimuli that predicted rewards with different magnitudes, probabilities, or cost (number of lever presses required to obtain the reward). The majority of cells in these areas coded two or more reward parameters, but a number of neurons in all three areas coded reward probability exclusively with increasing or decreasing firing rates. In addition, there were proportionally more neurons in the OFC that were tuned to a single reward parameter (such as probability).

By contrast, ACC neurons were more likely to reflect more than one decision parameter, potentially due to this area's role in passing value information to motor areas and assigning values to upcoming actions. This result is supported by previous work by Amiez et al. (2006), which showed dorsal ACC neurons integrated both reward probability and magnitude to code the expected value of reward-predicting stimuli. Interestingly, Kennerley et al. (2009) found that the latencies of separate neuronal reward probability signals in the ACC were longer than those of multiplexed value signals, suggesting the ACC receives its reward probability information from multiple regions.

PROBABILITY IN BASAL GANGLIA AND MIDBRAIN NEURONS

Electrophysiological studies of dopaminergic neurons in the substantia nigra (pars compacta) and ventral tegmental area have provided strong evidence that the brain codes reward probability. Fiorillo et al. (2003) used a Pavlovian conditioning paradigm with abstract visual cues, with each cue predicting a reward (0.15 ml of juice after 2 s) with a different probability ($p = 0.0$, $p = 0.25$, $p = 0.5$, $p = 0.75$, and $p = 1.0$). The monkeys showed increased anticipatory licking during cues predicting rewards with higher probabilities. Based on previous work on the phasic response of dopaminergic neurons to reward-predicting stimuli (Schultz, 1998) the researchers predicted that the phasic response to the cue should increase with increasing probability, and the response to reward should decrease with probability. This hypothesis was supported by the data (**Figure 2A**), with the phasic response fulfilling the necessary requirements of a reward prediction error reflecting probability as predicted by animal learning theory (Rescorla and Wagner, 1972).

The short latency of the dopaminergic neurons' response to reward-predicting stimuli (about 100 ms after stimulus onset) suggests that these cells carry probabilistic reward information at an early stage of any decision process. It has recently been proposed that a potential input to these cells is the globus pallidus (Hong and Hikosaka, 2008), with neurons of the interior segment of the globus pallidus (GPi) responding to reward expectancy at a similar latency to that of dopamine neurons. Arkadir et al. (2004) partly addressed this question by using the same range of reward probabilities as Fiorillo et al. (2003) and simultaneously recording from the external segment of the globus pallidus (GPe) in an instrumental conditioning task. Very few neurons of the GPe were found to respond exclusively to reward probability, with the majority responding to a combination of response direction and reward probability. The longer latency of these responses suggested that they may not be the source of reward probability signals observed at stimulus onset in dopamine neurons. A follow-up study using a probabilistic classical conditioning task with recordings from GPe, GPi, and substantia nigra pars reticulata (SNr) further characterized responses in these regions to reward-predicting cues (Joshua et al., 2009). This study confirmed that GPi neurons encoded reward probability with latencies of around 250 ms after cue onset, too slow to be the source of the dopaminergic signals demonstrated by Fiorillo et al. (2003). By contrast, SNr cells responded to increasing reward probability with increasing and decreasing firing rates in roughly equal proportions, with latencies in the range of 125 ms, more similar to the latencies of dopamine neurons.

Another potential source for the dopaminergic reward probability signal is the lateral habenula (primarily glutamatergic), for example via projection through the rostromedial tegmental nucleus (primarily GABAergic; Jhou et al., 2009; Hong et al., 2011). Neurons in this region code reward probability in an inverse manner to dopaminergic neurons, showing increased suppression of firing rates to stimuli predicting reward with increasing probability (**Figure 2B**; Matsumoto and Hikosaka, 2009). These neurons also increase their firing rates to stimuli that predict aversive events, suppressing dopaminergic activity in the substantia nigra pars compacta (Bromberg-Martin et al., 2010). The latency of response suppressions reflecting reward probability information in lateral habenula neurons is roughly comparable to that of excitatory responses in SNc and VTA cells. The antagonistic manner of reward and punishment probability coding in the dopaminergic and lateral habenula neurons suggests that downstream structures

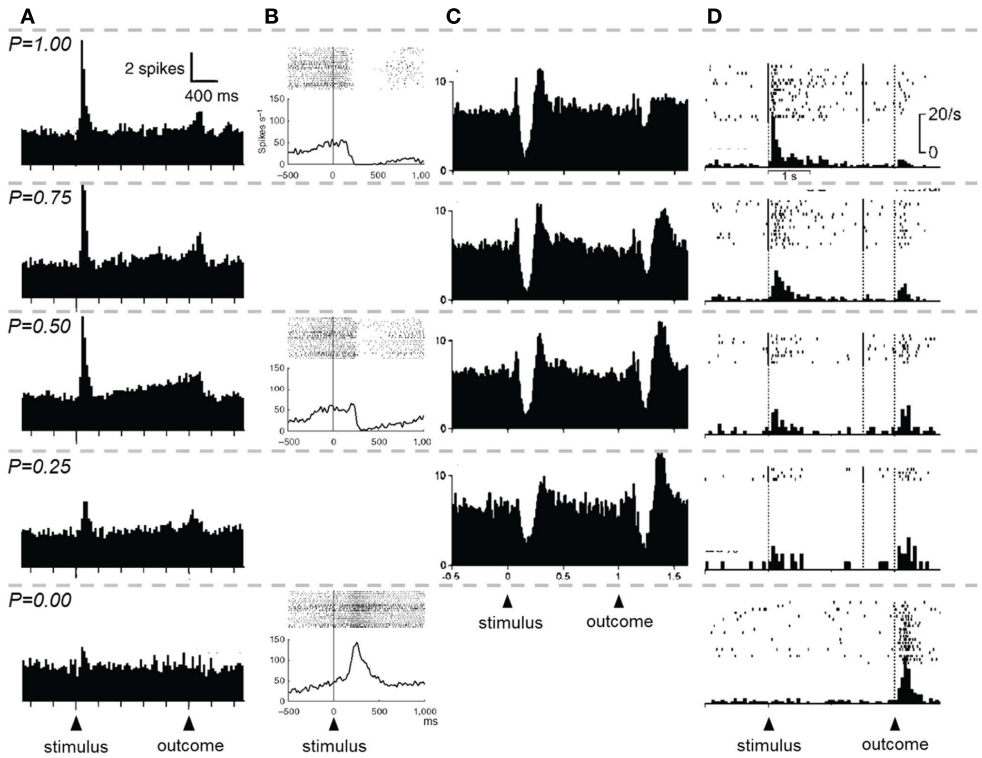

FIGURE 2 | Neuronal responses to reward probability, as demonstrated in four separate experiments. The descending rows represent trials with decreasing reward probability. Each column contains data from a separate experiment. **(A)** Population responses of dopaminergic neurons of the substantia nigra pars compacta and ventral tegmental area during a Pavlovian conditioning task, as described in Fiorillo et al. (2003). As an abstract visual stimulus predicts reward with decreasing probability, the dopaminergic neurons' phasic response to the stimulus decreases. In addition a sustained response that increases until the time of reward encodes reward risk. **(B)** An example of the responses of a single cell in the lateral habenula during a similar task as described in [**(A)** from Matsumoto and Hikosaka, 2009]. Lateral habenula neurons typically show increased firing rates during the presentation of cues that predict reward with decreasing probability. The task did not include trials with 0.75 and 0.25 reward probabilities. **(C)** Population responses of tonically active neurons in the putamen, as recorded by Apicella et al. (2009). Stimulus-related reward probability information is encoded in the pause and initial peak of a fraction of tonically active neurons. In addition reward probability exerts strong modulation of suppression and subsequent rebound activity at the time of the outcome. **(D)** Oyama et al. (2010) recorded from the dorsal striatum of the rat, pairing auditory stimuli with reward in a similar paradigm to Fiorillo et al. (2003). Shown here is a single cell demonstrating analogous reward probability coding to dopamine neurons of the VTA and SN, with the absence of a sustained uncertainty response. Note that for $p = 0.00$, no stimulus was presented to the animal, but a free reward was delivered. All figures reprinted with permission.

may contain subpopulations of neurons that code probability for both rewarding and punishing outcomes. The amygdala has been shown to be one such structure, containing cells responsive to cues predicting rewards and punishments and emitting responses that may be modulated by the probability of the outcome (Belova et al., 2007; Bermudez and Schultz, 2010a) as well as being sensitive to reward magnitudes (Bermudez and Schultz, 2010b).

Two of the most-discussed regions that are innervated by dopaminergic neurons are the striatum and the prefrontal cortex (Haber, 2003). However, these structures at least indirectly also project to dopaminergic neurons. Indeed, if the source of reward probability signaling is the GPi as proposed by Hong and Hikosaka (2008), one would also expect to find such signals in the putamen and caudate and recent research has shown this to be the case. In the striatum, cholinergic tonically active neurons (TANs) in the primate putamen have primarily been the subject of investigation with regard to reward probability. These cells typically show suppression of their firing rates when dopaminergic cells show increased activity (Morris et al., 2004), with the level of suppression coding reward probability in classical conditioning tasks (**Figure 2C**; Apicella et al., 2009). In these cells, reward probability was found to be processed primarily at the time of reward delivery, with increasing suppression of firing rates when reward was delivered with low probabilities, an inverse of the typical dopamine response (and more like lateral habenula neurons' responses). However, when no reward was delivered, two populations of TANs showed divergent firing patterns. Some cells increased their suppression when reward was predicted with high probability (like dopaminergic midbrain cells) while others showed increasing activity to reward omission with increasing reward probability (like lateral habenula cells). The responses of these neurons are quite variable and appear to only code reward probability in Pavlovian rather than instrumental tasks (Apicella et al., 2011). One potential explanation for the fast latency of TAN suppression is that TANs and dopaminergic neurons are recruited in parallel during the processing of relevant reward information,

allowing dopaminergic input to modulate corticostriatal synapses during learning.

By contrast, single-unit recordings from the dorsal striatum in rats have shown responses to reward probability that are more analogous to dopamine than that of TANs. Oyama et al. (2010) recorded from the caudate nucleus while rats performed a similar task to the one used in Fiorillo et al. (2003), with rewards being paired with auditory stimuli at different probabilities. Upon stimulus onset, many neurons were found to code reward probability with increasing firing rates (**Figure 2D**). At reward delivery, the opposite pattern of activation was found. Interestingly, these neuronal responses to probability were invariant to the satiety of the animal, suggesting that caudate neurons code probability independently of the current state and do not reflect the subjective value of the stimulus (a finding that is reminiscent of veridical probability coding in the human striatum; Tobler et al., 2008).

RISK AS DISPERSION IN MIDBRAIN, POSTERIOR CINGULATE, AND ORBITOFRONTAL CORTEX

Neurons that encode the probability of upcoming rewards are present in the basal ganglia, and frontal and parietal cortex. Of these, it seems that the responses of subcortical structures code reward probability in a relatively straightforward manner at the time of a reward-predicting cue. The phasic response of dopaminergic neurons in particular to reward probability perfectly reflects the notion of a reward prediction error signal, implying that probability representations are built up by successive sampling of the reward environment. Fiorillo et al. (2003) also demonstrated that a more sustained response of dopamine neurons in the same probabilistic task reflected the degree of risk on each trial. In the task of Fiorillo et al. (2003) when the animal is presented with a stimulus predicting a reward with $p = 0$ or $p = 1$, either no reward (for $p = 0$) or a reward (for $p = 1$) will be received with certainty and risk (e.g., variance) is zero on these trials. Risk is maximal for stimuli predicting rewards with $p = 0.5$, as the animal is equally likely to receive a reward or nothing at all. Risk therefore follows an inverted U-shape as a function of increasing reward probability. Fiorillo et al. (2003) found that approximately 30% of reward probability encoding dopamine neurons showed a sustained response that scaled with the risk on a given trial (**Figure 2A**). The sustained responses followed the initial phasic reward probability response and increased gradually until the time of reward delivery. It also increased when probability was kept constant at $p = 0.5$ but the dispersion was increased by manipulating the magnitudes of the two possible outcomes. How this risk signal is interpreted by postsynaptic neurons remains to be explored. Schultz (2010) suggests that the phasic, relatively high frequency spiking of dopaminergic neurons that codes reward probability (and prediction error) may be communicated to postsynaptic neurons through the preferential activation of D1 receptors. By contrast, the sustained, low frequency uncertainty response may preferentially engage postsynaptic D2 receptors due to their high affinity.

Dopamine is unlikely to be the only monoamine neurotransmitter involved in the coding of risk. Long et al. (2009) manipulated the diet of rhesus macaques to rapidly deplete their tryptophan levels and thereby systemically lower serotonin levels. This manipulation made monkeys more risk seeking. In particular, they tended to choose risky options more often (the reward magnitude of the safe option had to be increased by 60% in order to achieve indifference) compared to control conditions with normal serotonin levels. In risk-free choices, reward magnitude discrimination remained unchanged. Thus, serotonin appears to specifically reduce the subjective value of risk.

Using a formal definition of risk, coefficient of variation, McCoy and Platt (2005) recorded from the posterior cingulate cortex of monkeys during a visual gambling task. The task involved making a choice between two targets, with one yielding a fixed reward (juice delivered for 150 ms) and the other yielding a risky reward (chance delivery of juice for more than or less than 150 ms, with a mean time of 150 ms). The variance of the risky target's juice delivery was increased to manipulate risk (i.e., the most risky target would deliver juice for 50 or 250 ms, whereas the least risky target delivered juice for 140 or 160 ms). In contrast to the majority of human studies using such a paradigm, it was found that monkeys significantly preferred risky options to safe options, and that this behavioral preference actually increased with risk. Moreover, the preference could not be explained by novelty. Posterior cingulate neurons increased their firing rates when monkeys chose a risky option, especially for choices when the target was in the neuron's receptive field (**Figure 3A**). Interestingly, a number of these cells showed increased firing rates preceding risky choices even during fixation periods, suggesting a role for the posterior cingulate in biasing eye movements to options with higher subjective value. This information may be subsequently passed on to posterior parietal cortex where evidence of the coding of relative subjective value of eye movements has been shown (Dorris and Glimcher, 2004; Sugrue et al., 2004).

Risk as dispersion and reward value responses were investigated in detail with single-unit recordings in the OFC by O'Neill and Schultz (2010). In this experiment, monkeys learned to associate different visual stimuli with three binary equiprobable outcome distributions that differed in reward variance. Providing the animal made a correct response, the stimulus associated with high risk reward distributions was followed by either 0.18 or 0.42 ml of juice. By contrast the low risk stimulus was followed by 0.27 or 0.33 ml of juice, and an intermediate risk stimulus was followed by 0.24 or 0.36 ml. Note that the expected value of these reward distributions was equal (0.3 ml). In addition to these risky distributions, they also tested the responses of orbitofrontal neurons to rewards that varied in magnitude but not risk.

When given a choice, the animals preferred increasingly risky options over safe options with the same expected value and responded more quickly to risk-predicting stimuli, suggesting that monkeys were risk seeking in this situation. In areas 11, 12, 13, and 14, 109 orbitofrontal neurons showed activity that increased or decreased with risk (both reward variance and SD) at various stages of the task, most prevalently at cue presentation and during reward delivery (**Figure 3B**). Most of these cells coded risk at one task epoch, but some coded risk at 2 or more task epochs. Because monkeys were risk seeking in this experiment, a monotonic increase in activity to increasing risk could also indicate a value response. The separate manipulations of value and risk used by O'Neill and Schultz (2010) allowed them to demonstrate the presence of both distinct and combined value and risk signals.

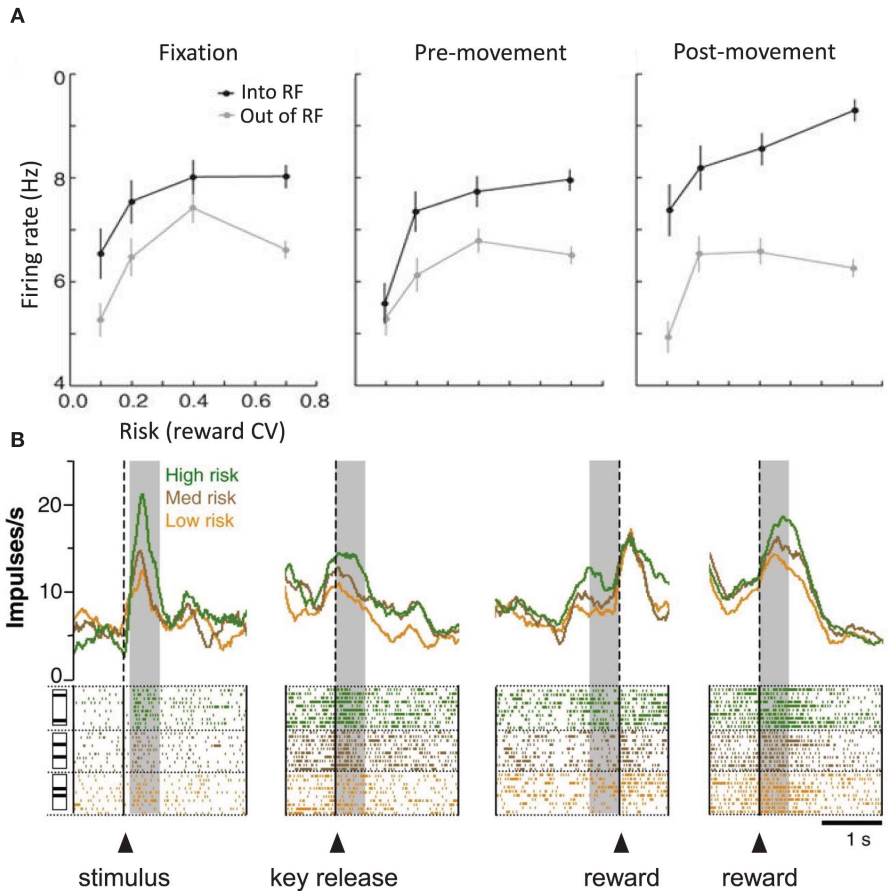

FIGURE 3 | Reward variance coding in posterior cingulate and orbitofrontal cortex. (A) McCoy and Platt (2005) recorded from the posterior cingulate cortex during a risky choice task. Neurons in this area were modulated by the reward variance (CV, coefficient of variation) of options inside and outside their respective receptive fields at various stages of the task, but the greatest modulation was observed at 200–400 ms after saccade onset. **(B)** O'Neill and Schultz (2010) found risk-related activity at various stages of the task in orbitofrontal neurons. OFC neurons code reward variance at short latencies after cue onset (∼100 ms) and continue to code variance even after the reward is delivered, and risk is resolved. The latencies of OFC risk coding neurons (faster than dopaminergic risk signals and the risk responses in the posterior cingulate and comparable to the latency of midbrain and basal ganglia reward probability signals) suggests the OFC may provide risk information to higher cortical regions in preparation for action selection. All figures reprinted with permission.

Yet, risk attitude appears to modulate responses of OFC neurons to risk as dispersion, particularly in situations of choice. Roitman and Roitman (2010) recorded from OFC neurons in rats. The animals performed in forced choice and free choice conditions. In free choice sessions, they chose freely between a risky (zero or four pellets, equiprobable) and a safe lever (two pellets for sure). In forced choice sessions, only one lever was available. Risk attitudes as measured in free choice situations were stable across days but differed across animals. In the majority of test sessions the animals were risk seeking (26 out of 42 sessions; 14 animals, each tested in 3 sessions), some were risk neutral (13 out of 42), and only few risk averse (3 out of 42). The activity of OFC neurons decreased or increased after the time of the outcome. These changes were not modulated by risk attitude in forced choice sessions but differed according to risk attitude in free choice sessions. In risk seeking (but not in risk neutral) animals, activation changes to the safe outcome were similar to those induced by the zero outcome of the risky option. Thus, a preference for risk coincided with more pronounced responses to the larger outcome of a risky option in choice situations.

A sizeable number of the neurons in the two studies (O'Neill and Schultz, 2010; Roitman and Roitman, 2010) continued to code risk even after the outcome was delivered to the animal, which is notable because the risk at this time point is zero. O'Neill and Schultz (2010) speculate that these risk signals after the outcome may represent an unsigned reward prediction error that could drive attention. Such a signal has recently been reported in the ACC of monkeys that receive outcomes following ambiguous gambles when reward probabilities are unknown or indiscernible to the animal (Hayden et al., 2011).

DECISION CONFIDENCE IN ORBITOFRONTAL CORTEX

Kepecs et al. (2008) extended the work on reward uncertainty by investigating the role of subjective decision uncertainty during

choice. In their task, rats were trained to enter a port and sample an odor, which contained information as to whether a reward would be delivered in an outcome port to the left or right of the odor port. The sampled odor was a binary mixture of two separate odorants (caproic acid and 1-hexanol), each of which was associated with either the left or the right side. The proportion of each odorant in the sample was altered (caproic acid: 1-hexanol ratios of 100:0, 68:32, 56:44, 44:56, 32:68, and 0:100%) in order to make it more or less difficult for the rat to decide which outcome port to visit. After the decision, the rats were required to wait for between 0.3 and 1 s before receiving a drop of water if their choice was correct. During this reward anticipation period, Kepecs et al. (2008) analyzed the activity of neuronal units in the lateral OFC. A large number of OFC neurons increased their firing rate with stimulus difficulty, with a smaller proportion showing the inverse encoding pattern. Although this pattern of firing is consistent with the dopaminergic risk signal, the neurons differed in their responses if the rats made correct or incorrect choices, suggesting that the OFC codes decision uncertainty calculated relative to the variance of perceptual information in a single trial, rather than reward risk, which can only be calculated after sampling outcomes over many trials. However, Kepecs et al. (2008) conclude that the decision uncertainty experienced by rats in their task covaries with reward probability and uncertainty (since the probabilities were only manipulated in the range of $p = 0.5$ to $p = 1$). Although the OFC is densely innervated by afferent fibers from dopaminergic midbrain, it remains to be seen if the OFC decision uncertainty signal is related to dopaminergic reward risk or probability signals. One speculative idea is that the OFC signal is driven by upstream neurons that maximally fire with coincident input from dopaminergic and lateral habenula neurons. Since these cells have been demonstrated to reliably respond in an opposite fashion to reward probability, neurons that summate over the output of both would be more likely to fire to cues predicting rewards at maximal risk.

CONCLUSION

The studies described in this review all demonstrate that behaviorally relevant reward parameters such as probability and variance are encoded at the neuronal level and in a distributed fashion. Many of the implicated regions are directly connected, suggesting that a network contributes to the processing of probability and risk. Measuring firing activity from single neurons requires the use of single or multiple microelectrodes to detect discharges. Together with well-controlled behavioral paradigms this technique allows us to correlate neuronal activity with behavior at extremely high temporal resolution. However, due to restricted sampling, electrophysiological recordings are somewhat difficult to interpret on a larger scale. The technique usually targets very small volumes of brain tissue and limited numbers of neurons, and online searching for neurons showing task-related activity may undermine the ability to define specific roles of distinct brain regions or nuclei. There also remains the possibility that reward uncertainty signals are coded in a distributed fashion across networks of neurons, which would be difficult to ascertain in behaving animals using current techniques.

Many of the questions raised by single-unit recordings in reward uncertainty paradigms are beginning to be addressed by researchers. There are however many exceptions and gaps in our understanding, providing many opportunities for further research. Future research may wish to address whether higher-order risk terms and ambiguity are processed in single neurons and the degree to which reward uncertainty signals are processed in a subjective or objective manner. The temporal development of risk signals in the brain remains a complex issue (**Table 1**), especially with respect to where stimulus identity is decoded and the relevant reward parameters passed onto regions generating appropriate behavioral output. One potential candidate as the source of reward probability and risk signals is the amygdala (Herry et al., 2007), which has been shown to distinguish the valence of conditioned stimuli at latencies as short as 20–30 ms (Quirk et al., 1995). At early stages of processing, reward uncertainty signals appear to be coded separately from other information, consistent with economic theories suggesting that the statistical parameters of reward distributions are detected and represented separately in a mean–variance approach to expected reward processing (Boorman and Sallet, 2009). At later stages the signals are multiplexed with other reward signals and often combine sensory and motor preparatory information.

One problem of comparing the current findings relates to the differences in the behavioral tasks used in different studies. For example, the pathways responsible for passing reward uncertainty signals to output structures may differ depending on the sensory modality of stimuli or whether the task involves Pavlovian or instrumental conditioning. This may particularly apply to

Table 1 | Example latencies (where available) of single units measured in experiments manipulating reward probability and variance.

Uncertainty parameter	Region/structure	Response latency	Experiment
Reward probability	Ventral tegmental area, substantia nigra pars compacta	∼100 ms	Fiorillo et al. (2003)
	Lateral habenula	∼100 ms	Matsumoto and Hikosaka (2009)
	Substantia nigra pars reticulata	∼125 ms	Joshua et al. (2009)
	Globus pallidus, internal segment	200–300 ms	
	Globus pallidus, external segment	200–300 ms	
	Putamen	<100–250 ms	Apicella et al. (2009)
	Caudate	<100 ms	Oyama et al. (2010)
Reward risk	Orbitofrontal cortex	∼100 ms	O'Neill and Schultz (2010)
	Ventral tegmental area, substantia nigra pars compacta	Reward-locked (∼600 ms)	Fiorillo et al. (2003)
	Posterior cingulate cortex	300 ms +	McCoy and Platt (2005)

striatal neurons that code reward-related information dependent on whether or not an action is required or in choice versus no choice situations (Hassani et al., 2001; Kawagoe et al., 1998; Lau and Glimcher, 2008). The network propagation of these signals could be further elucidated by employing at least three techniques. Firstly, simultaneous recording of (anatomically well defined) pre- and postsynaptic structures would potentially allow researchers to identify the flow of reward uncertainty information. Stimulation of one or more brain regions while simultaneously recording from another could also further enhance our understanding of information flow. Finally, a technique that allows the selective excitation or suppression of distinct classes of neurons within an area would potentially offer researchers a very powerful tool to assess the informational flow of reward uncertainty information. Optogenetics is one such method that was recently used to modulate dopaminergic activity in a reward-based paradigm in the mouse (Tsai et al., 2009).

Understanding the likelihood of a future reward or predicting variability in the quality of potential rewards seems to be just as important as predicting reward magnitudes to animals. The effects of uncertainty are well known to affect the foraging behavior of many species so it is perhaps not surprising that these higher-order reward parameters are coded in large numbers of cells throughout the brain. Additionally, the fact that reward uncertainty is coded in the basal ganglia and midbrain, structures that are largely conserved throughout the vertebrates, supports the adaptive importance of such signals.

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Ambiguity aversion in rhesus macaques

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People generally prefer risky options, which have fully specified outcome probabilities, to ambiguous options, which have unspecified probabilities. This preference, formalized in economics, is strong enough that people will reliably prefer a risky option to an ambiguous option with a greater expected value. Explanations for ambiguity aversion often invoke uniquely human faculties like language, self-justification, or a desire to avoid public embarrassment. Challenging these ideas, here we demonstrate that a preference for unambiguous options is shared with rhesus macaques. We trained four monkeys to choose between pairs of options that both offered explicitly cued probabilities of large and small juice outcomes. We then introduced occasional trials where one of the options was obscured and examined their resulting preferences; we ran humans in a parallel experiment on a nearly identical task. We found that monkeys reliably preferred risky options to ambiguous ones, even when this bias was costly, closely matching the behavior of humans in the analogous task. Notably, ambiguity aversion varied parametrically with the extent of ambiguity. As expected, ambiguity aversion gradually declined as monkeys learned the underlying probability distribution of rewards. These data indicate that ambiguity aversion reflects fundamental cognitive biases shared with other animals rather than uniquely human factors guiding decisions.

Keywords: ambiguity, risk, risk aversion, risk seeking, uncertainty, macaque

INTRODUCTION

Risk and ambiguity are two forms of uncertainty distinguished by the amount of uncertainty associated with the likelihoods of their outcomes. Whereas the outcome of a risky choice is drawn from a distribution known by the decision-maker, the outcome of an ambiguous choice is drawn from an unknown distribution. The distinction between the two is often illustrated by the Ellsberg paradox, in which the subject chooses between two urns containing colored balls: the risky urn contains an equal number of blue (high reward) and red (low reward) balls while the ambiguous urn contains an unknown number of each ball. A ball is drawn blindly from the chosen urn and a large or small reward is given, depending on the color of the ball. Even when informed that the ratio of balls from the second urn is selected at random, people consistently prefer known probability distributions to unknown ones – even if the unknown has greater expected value (Ellsberg, 1961).

Economists and psychologists have long recognized that these two forms of uncertainty have dissociable influences on behavior, so a complete explication of decision-making under uncertainty must encompass both (Keynes, 1921; Knight, 1921; Ellsberg, 1961; Gardenfors and Sahlin, 1982; Frisch and Baron, 1988; Camerer and Weber, 1992; Fox and Tversky, 1995; Yu and Dayan, 2005). A similar distinction, between expected and unexpected uncertainty, features prominently in learning theory (Yu and Dayan, 2002; Dayan and Yu, 2006). Far from a mere economic and mathematical curiosity, the distinction between different forms of uncertainty has important implications for business, medicine, microeconomic theory, and neuroscience (Knight, 1921; Epstein and Wang, 1994; Hsu et al., 2005; Huettel et al., 2006).

Humans reliably prefer risky options to ambiguous ones in a variety of laboratory and real-world situations, and will pay a premium to avoid ambiguity (Einhorn and Hogarth, 1985; Curley et al., 1986; Fox and Tversky, 1995). Precisely why people avoid ambiguity remains unclear. Several proposed explanations focus on uniquely human factors, including verbally representing probabilities, the need to justify one's decision (Curley et al., 1986), the assumption that the "deck is stacked" by one's opponent (Kühberger and Perner, 2003), and the desire to avoid public embarrassment (Heath and Tversky, 1991). Since ambiguity aversion has never been demonstrated experimentally in any animal, these explanations remain to be fully tested.

To address these issues experimentally, we probed the preferences of monkeys amongst options characterized by different degrees of uncertainty about the probability of obtaining a large reward if chosen. Here we use the terms risky and ambiguous to refer to options whose reward probabilities are either fully specified or obscured, although we note that knowledge about probability more likely varies along a continuum in real life situations. We found that monkeys, like humans, are averse to ambiguity, and that this aversion increases parametrically with degree of uncertainty. The preferences observed in monkeys closely matched those found in humans in a nearly identical task. These findings have important implications for understanding economic decision-making, uncertainty, and learning, as well as the evolution of human cognitive biases.

MATERIALS AND METHODS

All experiments have been approved by the Duke University IACUC and IRB, and confirm to relevant regulatory standards. Informed consent was obtained from human subjects.

MONKEY BEHAVIORAL TECHNIQUES

All animal procedures were approved by the Duke University Institutional Animal Care and Use Committee and were designed and conducted in compliance with the Public Health Service's Guide for the Care and Use of Animals. Four male rhesus monkeys (*Macaca mulatta*) served as subjects. Prior to the beginning of experiments, a small head-holding prosthesis was implanted in all animals using standard surgical techniques to permit high-resolution measurement of eye position and intracerebral neurophysiological recording (not reported here). Six weeks later, animals were habituated to training conditions and then trained to perform oculomotor tasks. To motivate behavior, monkeys were placed on controlled access to fluid outside of experimental sessions and task performance was reinforced with liquid rewards.

Horizontal and vertical eye positions were sampled at 1000 Hz by an infrared eye-monitoring camera system (SR Research, Osgoode, ON, Canada). Stimuli were controlled by a computer running Matlab (Mathworks, Natick, MA, USA) with Psychtoolbox (Brainard, 1997) and Eyelink Toolbox (Cornelissen et al., 2002). Visual stimuli were colored rectangles on a computer monitor placed directly in front of the animal and centered on his eyes. A standard solenoid valve controlled the duration of juice delivery. Reward volume was 67, 200, or 333 μL in all cases.

Every trial began when two bars and one potential occluder appeared (**Figure 1A**). Each bar was divided into a blue portion and a red portion, or was completely gray (indicating a 100% probability of a medium sized reward; **Figure 1B**). For the risky targets, the blue portion, always on top, indicated the probability that choosing that bar would yield a large reward (**Figure 1C**). The red portion indicated the probability that choosing that bar would yield a small reward. All probability bars were 80 pixels wide and 300 pixels tall. The occluder was either 150, 225, or 300 pixels tall (depending on the level of ambiguity; see below) and always 200 pixels wide.

The monkey had 1 s to inspect these stimuli. Casual observation showed that monkeys reliably looked at both bars during this period. Next, a small yellow fixation point appeared at the center of the monitor. Once eye position was aligned with this point (±0.5°), the monkey was required to maintain fixation for 1 s. The fixation point was then extinguished, and two response targets appeared. These were small yellow squares overlaid on the center of the probability bars. The monkey then had to select one of these bars by shifting gaze to it (±3°). Following the saccade, the gamble was immediately resolved by the delivery of a reward. All task stimuli were then extinguished. The reward probabilities for the ambiguous option were never revealed.

The cyan occluder appeared on all trials. On two-thirds of trials, the occluder appeared at a random location on the screen, and sometimes covered part of the bar without obscuring information about probabilities (**Figure 1D**). On these trials, the horizontal position of the occluder was randomly jittered. On one-third of trials (ambiguous trials), the occluder obscured the center of one of the bars at the intersection of the blue and red portions (**Figure 1E**). The height of the occluder on the ambiguous option was equally likely to be 150, 225, or 300 pixels; the resulting occluders were called low, medium, and high ambiguity occluders, respectively.

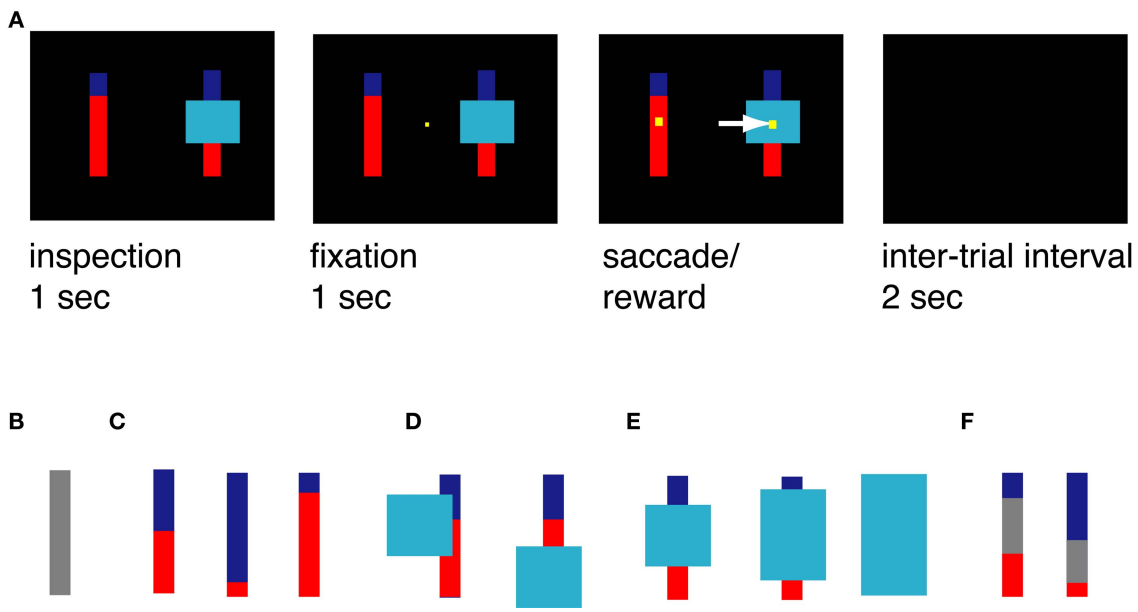

FIGURE 1 | Task and stimuli. (A) Task design. Monkeys had 1 s to freely inspect the bars. When a small yellow fixation square appeared, they had to look at it and maintain fixation for 1 s. The square then disappeared, and they were free to shift gaze to one of the two targets. They then received the appropriate reward and waited through a short inter-trial interval (ITI). **(B–F)** Examples of stimuli used in this task. **(B)** Gray bar, certain stimulus, yields 200 μL juice. **(C)** Examples of risky options. Blue/red bars yield either 333 or 67 μL juice; probability can vary from 0 to 100%. In this example, probabilities of large reward are 50, 88, and 17%, corresponding to the size of the blue portion of the bar. **(D)** Example of risky option with partially covering occluder that did not render probabilities ambiguous. **(E)** Ambiguous options. The size of the occluder rendered the bar either low, medium, or high ambiguity (left to right). **(F)** Examples of stimuli used in triple bar control task.

The probability that the ambiguous option would provide a large reward was drawn from a uniform distribution of the probabilities within the range of those obscured by the occluder, and an outcome was chosen accordingly. This is mathematically equivalent to a 50% probability of a large reward on all ambiguous trials, and the expected value of the ambiguous option was always 200 μL. On a small minority of risky trials, the occluder covered only a portion of the bar; on such trials, the border between the blue and red regions was visible, and these trials were considered risky options in all analyses. Finally, on 10% of trials (chosen randomly), a gray bar appeared instead of one of the two red/blue bars; this option had a 100% probability of a medium sized reward (200 μL) and was considered certain.

THE TRIPLE BAR CONTROL TASK

We were concerned that monkeys would adopt a strategy such as "look for the largest blue bar" that would bias them away from the occluded options. We performed a control experiment to test for this possibility (**Figure 1F**). In the Triple Bar control, the two bars were each divided into three sections – blue, gray, and red – that independently indicated the probability of a large, medium, or small reward. As in the standard task, the amount of blue and red indicated the probabilities of obtaining the large (333 μL) and small (67 μL) rewards, respectively. In this control task, the size of the gray portion of the bar indicated the probability of obtaining a medium reward (200 μL). As in the standard task, all probabilities were drawn from a uniform distribution. To reduce the possibility that the monkeys would learn this task and treat it differently from the standard task, we recorded behavior on only one short (~500 trials) session with no training. During the Triple Bar control, the occluder never covered the bars.

ANALYSES

We calculated the point of subjective equivalence (PSE) between risky and ambiguous options (Deaner et al., 2005). We first fit a cumulative Gaussian function to the monkeys' choices of risky over ambiguous options, as a function of the expected value of the risky option. (Because only two outcomes were used, the probability scaled linearly with the expected value, so these are interchangeable in this task.) We used a least-squares minimization method (Matlab Statistics Toolbox) with four free parameters: mean, variance, gain, and bias. To estimate standard errors on PSEs, we calculated the standard error of a distribution of 10 PSEs calculated on 10 subsets randomly selected (without replacement) from the original data. The resulting PSE provides a revealed preference measure of value assigned to the ambiguous option. Any PSE below 50% reflects a preference for the risky option and an aversion to the ambiguous option.

HUMAN BEHAVIOR

All procedures were approved by the Duke University Institutional Review Board. Behavior of 10 human participants in a human analog of the task was analyzed. Participants were recruited from the undergraduate and graduate population of Duke University. No participants had extensive psychological, neuroscientific, or economic training. Participants were merely told to maximize the number of points earned on each trial. All parameters of the task were identical with the following exceptions. No juice rewards were given. Participants obtained 50, 140, or 230 points; these values corresponded to the small, certain, and large rewards in the monkey task. Rewards were indicated at the end of each trial with text on the monitor for 1 s. Cumulative score was indicated with text on the monitor for 3 s every 10 trials. Participants performed three blocks of 250 trials. Participants were not required to fixate, but pressed the space bar on the keyboard to initiate trials. Participants did not indicate choices with saccades, but by pressing the left and right arrows on the keyboard.

Participants were read the following script before beginning. "On each trial, you will choose between two options. Each option is represented by a bar, and can pay either 50, 140, or 230 points. The colors of the bars give information about the probabilities of these two possibilities. When the options appear, press the space bar and then either the left or right arrows. Your goal is to get the most points you can. This is all I can tell you right now. Good luck." Participants were asked to explain their interpretations of the meaning of the stimuli at the end of the entire session by an undergraduate researcher who was blind to the hypotheses of the experiment. All participants were paid $10.

RESULTS

All four monkeys preferred risky options to ambiguous options (**Figures 2A,B**). Although monkeys were more likely to choose the risky option over the ambiguous option the greater the expected value of the risky option, there was a strong overall bias toward the risky option (**Figure 2A**). The PSE measures the probability of large reward for the risky option for which the monkey chooses the ambiguous option equally often; a PSE below 50% indicates ambiguity aversion (Deaner et al., 2005; Hayden et al., 2007). Monkeys' average PSE for ambiguous options was a risky option with 30% chance of large reward, meaning that they required a premium of 53 μL of juice to choose the ambiguous option. This amount is substantial – 15.9% the size of the large reward, and 80% the size of the small reward. All four monkeys had PSEs less than 50% [mean 29.9%, $t(3) = -4.4$, $p = 0.02$, **Figure 2B**]. These data demonstrate that monkeys distinguish degrees of uncertainty, and, like humans, are reluctant to choose ambiguous gambles. Monkeys showed greater aversion to the high ambiguity option than the medium and low ambiguity options (**Figure 2C**, bootstrap *t*-test, $p < 0.001$ in both cases). This preference pattern indicates that monkeys were not simply reluctant to choose an obscured bar, which may have appeared to be an entirely novel stimulus, but rather were systematically averse to the level of uncertainty associated with the ambiguous option.

To be certain that our task tapped into traditional ambiguity aversion, we examined behavior of 10 human participants in an analogous task for monetary rewards using the same test stimuli, without providing instructions about the relationship between the bar stimuli and reward probabilities (**Figure 3**). We found that people, like monkeys, preferred risky options to ambiguous options (population PSE 42, $n = 7500$ trials, bootstrap *t*-test $p < 0.001$). The distribution of individual PSEs was also significantly biased toward ambiguity aversion (mean of individual PSEs = 41.6, $p = 0.019$). We observed a significant preference for risky options in 5/10 participants and a preference for ambiguous options in two participants ($p < 0.05$, bootstrap *t*-test). No significant changes in preferences

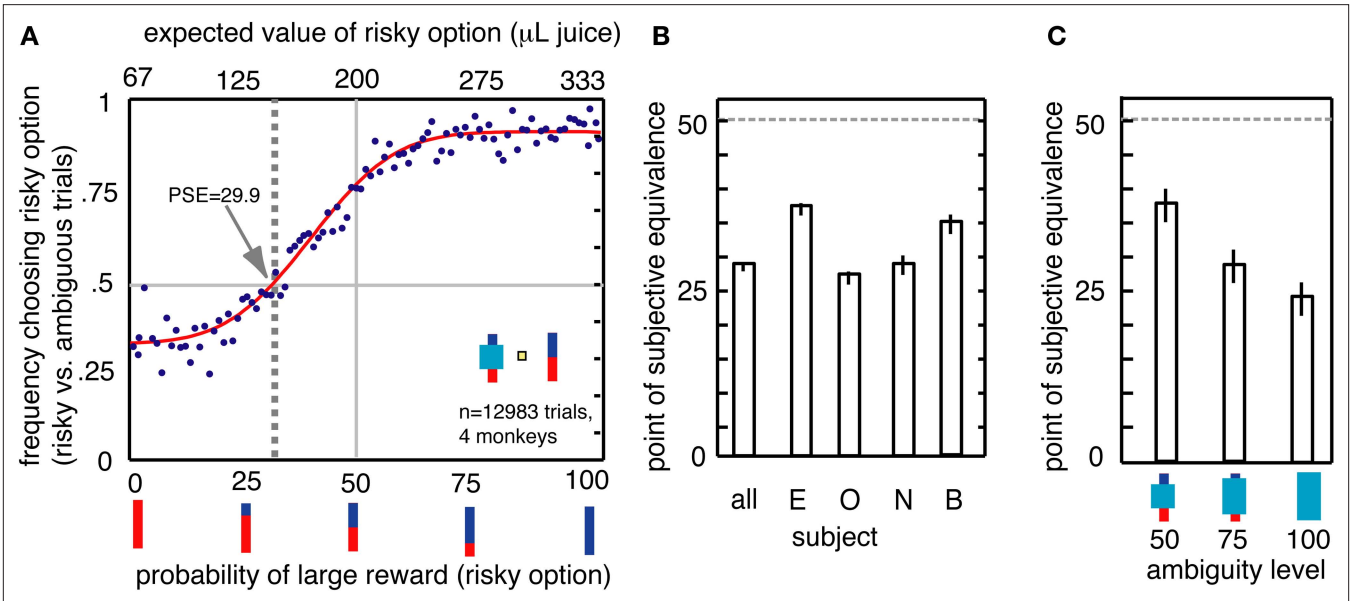

FIGURE 2 | Ambiguity aversion in monkeys. (A) Behavioral preference for risky over ambiguous options. Dots represent frequency of choosing risky option for each of the 100 individual risky probabilities on risky vs. ambiguous trials. Line is a best-fit cumulative Gaussian. The point of subjective equivalence (PSE, shown by vertical gray dashed line) indicates values at which subjects were indifferent to the two options. The PSE is smaller than 50, indicating that monkeys were ambiguity-averse. **(B)** Individually, all four monkeys showed ambiguity aversion (PSE significantly less than 50). **(C)** Ambiguity aversion varied parametrically with degree of ambiguity. Greatest aversion was observed for high uncertainty options.

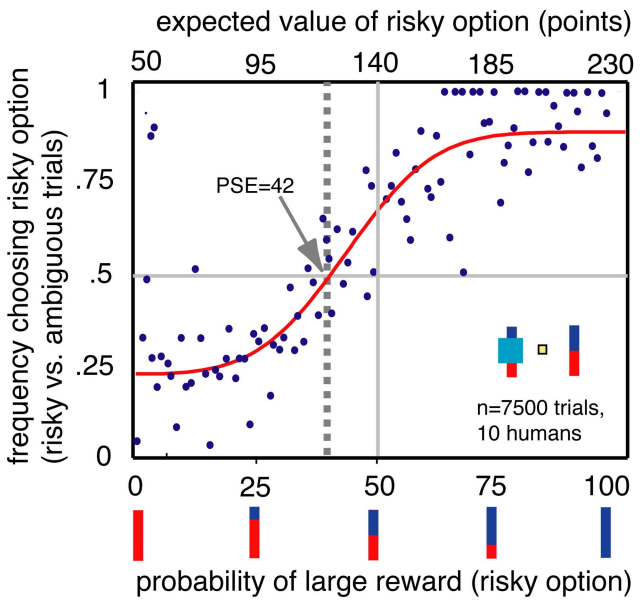

FIGURE 3 | Humans, like monkeys, preferred options with known probabilities. Conventions as in **Figure 2A**.

were observed over the course of the single session (three blocks of trials, one-way ANOVA, $p > 0.5$). Preferences for certainty were weaker in human participants than in monkeys. This distinction may reflect differences in motivation, familiarity with abstract probabilities or familiarity with the task. To assess our human participants' motivations, an experimenter naïve to the goals of the study debriefed them in detail. When asked to explain what they noticed about the task, all participants stated that they quickly came to recognize that the occluder obscured information about outcome probabilities even though they had not been told this fact. The similarity between human and monkey performance suggests that individuals of both species readily interpreted the bar stimuli as reward probability cues and that the cyan rectangle occasionally obscured such information.

On a subset of trials, the occluder partially covered the bar, but did not cover the border between the blue and red sections. On these trials, information about probabilities was available, and so no ambiguity aversion should be observed. Indeed, we observed no difference in monkeys' preferences for these partially covered bars and fully uncovered bars (**Figure 4A**, no difference, $p > 0.4$, bootstrap *t*-test). We further tested this idea of novelty aversion with a behavioral control performed near the conclusion of data collection. On 50% of trials, the occluder was magenta, making it a novel stimulus compared to the normal cyan occluder. We found that monkeys' preferences for options obscured by the two differently colored occluders were indistinguishable statistically (**Figure 4B**, $p > 0.5$, binomial test).

If monkeys learn about the underlying probabilities of ambiguous options, PSEs should eventually converge on 50%. For two of the monkeys in this study (monkeys E and O), we continued to collect data for several months. PSEs for these two monkeys gradually approached indifference after 40–50 individual behavioral sessions (**Figure 4C**). PSEs in the final 10 sessions were significantly higher than those during the first 10 sessions ($p < 0.05$ for both animals individually, bootstrap *t*-test) and were not significantly different from 50% ($p > 0.3$ for both animals; binomial test). Despite this evidence for learning, monkeys never developed an outright preference for the ambiguous option during the course of this experiment.

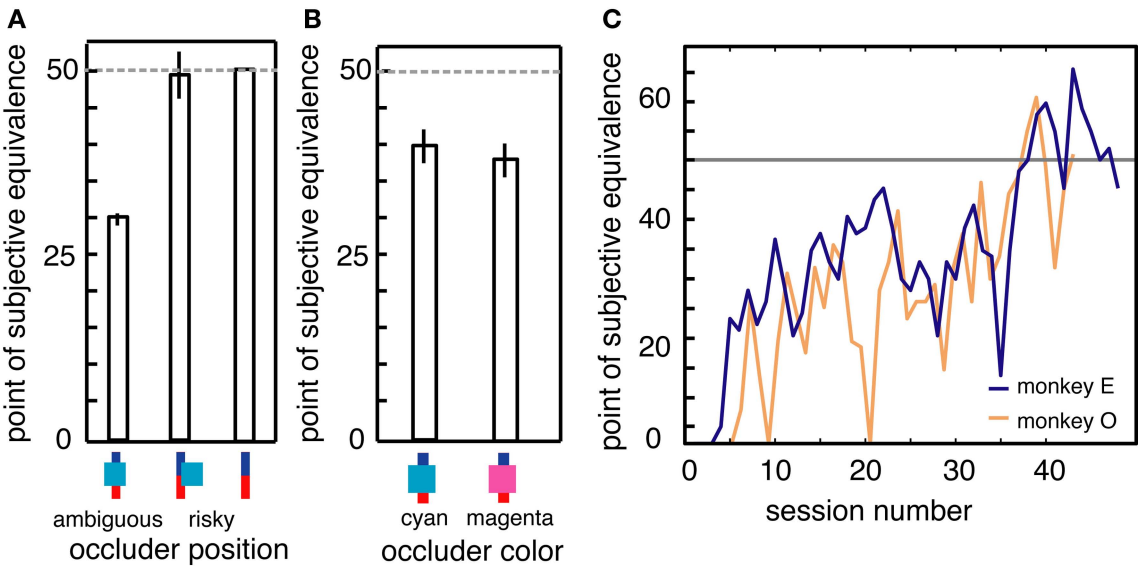

FIGURE 4 | (A) Monkeys did not avoid occluders that did not obscure reward probability information. **(B)** Monkeys treated a new, magenta occluder the same as the previously encountered cyan occluder, demonstrating that preference do not reflect novelty aversion. **(C)** Monkeys learned reward probability distributions associated with ambiguous options over time. PSEs for the two most extensively tested monkeys, O (orange) and E (blue), plotted over the course of behavioral sessions. PSE indicates average level of aversion to ambiguous options for a session; values below 50% represent aversion, values at 50% (indicated by horizontal gray line) represent neutrality. Horizontal axis refers to recoding session number. Each session consisted of ~1500–2500 trials.

Although not the main focus of our study, we also examined choices between risky and certain options. All four monkeys significantly preferred risky options to certain options with the same expected value ($p < 0.001$ in all cases). On average, monkeys sacrificed a potentially larger reward of 71 μL of juice to choose the risky option instead of the certain option, and preferred 50:50 risky options to certain options on 72% of trials. These findings are consistent with previous studies showing that rhesus macaques choose risky options about 75% of the time over certain options in an uncued gambling task with highly familiar probability contingencies (McCoy and Platt, 2005; Hayden et al., 2008a,b). Our task occasionally pitted the ambiguous option against the certain option. Monkeys weakly preferred the ambiguous option to the certain option (they chose the ambiguous option on 58.9% of these trials, binomial test, $p = 0.0024$). This preference was weaker than the monkeys' preference for the risky option over the certain option (71% of trials). The observed preference for the ambiguous and risky options over the certain option may reflect exploration strategies aimed at learning the underlying probability distributions (Hayden et al., 2008a; Pearson et al., 2009).

Several additional control analyses and experiments confirm that ambiguity aversion does not reflect other processes such as difficulty in distinguishing the stimuli or simple reinforcement learning. First, ambiguity aversion did not arise from poor discrimination of the bars used to symbolically cue reward probability. Monkeys were better than chance at distinguishing similar bars that differed by as few as 4% (12 pixels on the monitor, $p = 0.026$ for 4%, $p < 0.001$ for all larger differences, bootstrap t-test, **Figure 5A**). This figure indicates monkeys' preference behavior when choosing between pairs of risky options, in the absence of an ambiguous one. Preferences for larger differences followed a simple psychometric curve. This plot thus also demonstrates that the monkeys were less likely to choose the inferior (i.e., less probable) option as the penalty grew. We observed no systematic changes in preferences between two risky options over the course of behavioral training.

Second, ambiguity aversion did not simply arise from reinforcement learning mediated associations of the bar stimuli. In principle, monkeys could derive a value for each of the 100 different bar patterns based on an integrated reward history, and choose based on these reward associations (Thorndike, 1911). To address this concern, we analyzed preferences for the bars the first time each target appeared. Because monkeys confused targets that were within 3 pixels of each other (see above), we restricted this analysis to the first time a stimulus or any other stimulus that could be confused with it appeared. These data therefore all originate from the first day of behavioral training with the risky bars. Before this, monkeys had been trained only on all-blue and all-red certain bars. This restriction limited us to 14 or 15 trials total for each monkey, and makes this test very conservative. Nonetheless, we found that even on these early trials, three of the four monkeys expressed a significant preference for the option with greater EV ($p < 0.03$ in all cases, bootstrap t-test). This analysis provides strong evidence that monkeys generalized the meaning of the blue and red bars to mixed bars.

Third, monkeys did not merely adopt a strategy such as "look for the largest blue bar" that would bias them away from the occluded options (including the ambiguous ones). The fact that monkeys did not avoid partially occluded options that did not fully obscure reward probability information speaks to this issue (**Figure 4A**). To directly test this possibility, we performed a control experiment in which the two bars were each divided into three sections – blue, gray, and red – which indicated the probability of a large, medium,

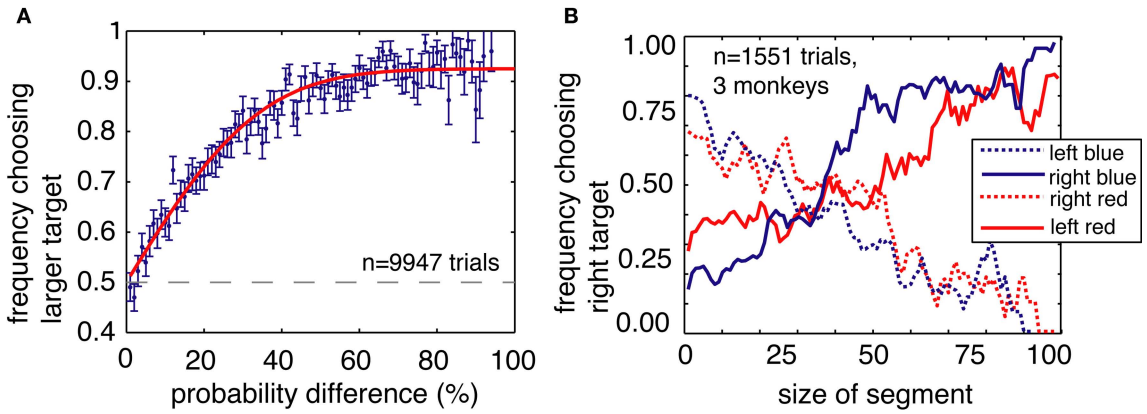

FIGURE 5 | Ambiguity aversion is not an artifact of poor stimulus discrimination or heuristic strategies. (A) Stimulus discrimination. The *y* axis gives the monkeys' probability of choosing the target with the greater expected value (the bluer bar) on risk–risk trials, as a function of the difference in amount of blue (or red) between the two available targets (*x* axis). **(B)** Plot of the probability of choosing the rightward target, as a function of the size of the red and blue portions of the bars on the left and the right (as indicated in the legend to the right of the plot). Horizontal axis corresponds to size of either red or blue bar portion. Vertical axis indicates probability of choosing right-side target. Preferences vary roughly with both blue and red bar portions, indicating that monkeys attend to both in their decisions. Data is smoothed for presentation.

or small reward, respectively (**Figure 5B**). We reasoned that if the monkeys simply associated the blue option with large reward, and selectively chose the option with the larger blue area, then behavior would not depend on the relative amounts of red and gray. By the same token, if the monkeys simply associated the color red with small reward, then behavior would not depend on the relative amounts of blue and gray. However, if the monkeys understood that the relative size of the red and blue sections corresponded to outcome probabilities, they would rapidly generalize to a three-color bar.

We performed this task on three of the four monkeys. As in the standard task, the amount of blue and red indicated the probabilities of obtaining the large (333 μL) and small (67 μL) rewards, respectively. In this control task, the size of the gray bar indicated the probability of obtaining a medium sized reward (200 μL). As in the standard task, all probabilities were drawn from a uniform distribution. To reduce the possibility that the monkeys would learn this task and thus treat it differently from the standard task, we recorded behavior on only one brief (~500 trials) session with no training. We found that choices varied lawfully as a function of both blue and red sections, indicating that monkeys attended to the lengths of both (**Figure 3**). The results of this control experiment demonstrate that monkeys readily use information about probabilities presented in an abstract and continuously varying form, and that they interpret occluders as obscuring that information.

DISCUSSION

Our findings demonstrate that monkeys prefer explicit information about reward probability distributions and avoid options in which this information is obscured – just as humans do. Moreover, monkeys' behavior in this task closely matched that of humans in a very similar task; human participants interpreted their task in a manner consistent with conventional definitions of risk and ambiguity (Ellsberg, 1961; Frisch and Baron, 1988; Camerer and Weber, 1992; Fox and Tversky, 1995). These findings indicate that non-human animals, like humans, are sensitive to the distinction between risk and ambiguity, and prefer options with full information. Because it is impossible to know the content of the monkeys' thoughts, we cannot be completely certain that the monkeys in our task understood the concepts of probabilities and relative degrees of uncertainty. Nonetheless, the monkeys' pattern of performance, and their behavior on the controls, is most straightforwardly interpreted in this context.

Uncertainty is a ubiquitous and inevitable aspect of decision-making. The distinction between risk and ambiguity, and between expected and unexpected uncertainty, is a fundamental and natural one (Knight, 1921; Ellsberg, 1961; Becker and Brownson, 1964; Camerer and Weber, 1992; Yu and Dayan, 2005). For example, canny decision-makers should more fully engage learning processes when confronted with unexpected uncertainty (Frisch and Baron, 1988; Yu and Dayan, 2005; Dayan and Yu, 2006). Thus, it should not be surprising that monkeys readily make this distinction.

Indeed, our findings imply that the cognitive processes motivating human preferences for certainty are shared with non-human primates. Furthermore, our data endorse the idea that ambiguity aversion does not reflect uniquely human faculties or motivations such as language, the need to justify one's decision, aversion to competition with a skilled opponent, the desire to avoid the embarrassment or regret of a decision that is later revealed to have been unwise, or feelings of competence within a domain of knowledge (Curley et al., 1986; Heath and Tversky, 1991; Kühberger and Perner, 2003).

Monkeys' simultaneous preference for risk and aversion to ambiguity seems surprising from an economic perspective (Ellsberg, 1961; Becker and Brownson, 1964; Frisch and Baron, 1988; Camerer and Weber, 1992; Fox and Tversky, 1995). Because unspecified probabilities are in some sense a form of compounded uncertainty, some economists have proposed that ambiguity aversion in humans may be an extension of risk aversion (Frisch and Baron, 1988). By contrast, our results suggest that monkeys'

avoidance of the ambiguous option is not simply a general aversion to uncertainty. Instead, our findings are consistent with recent studies demonstrating that risk preferences and ambiguity preferences are mediated by distinct psychological and neural mechanisms (Hsu et al., 2005; Huettel et al., 2006). Further research will be necessary to determine whether these specific mechanisms are shared with non-human primates.

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Decision salience signals in posterior cingulate cortex

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Despite its phylogenetic antiquity and clinical importance, the posterior cingulate cortex (CGp) remains an enigmatic nexus of attention, memory, motivation, and decision making. Here we show that CGp neurons track decision salience – the degree to which an option differs from a standard – but not the subjective value of a decision. To do this, we recorded the spiking activity of CGp neurons in monkeys choosing between options varying in reward-related risk, delay to reward, and social outcomes, each of which varied in level of decision salience. Firing rates were higher when monkeys chose the risky option, consistent with their risk-seeking preferences, but were also higher when monkeys chose the delayed and social options, contradicting their preferences. Thus, across decision contexts, neuronal activity was uncorrelated with how much monkeys valued a given option, as inferred from choice. Instead, neuronal activity signaled the deviation of the chosen option from the standard, independently of how it differed. The observed decision salience signals suggest a role for CGp in the flexible allocation of neural resources to motivationally significant information, akin to the role of attention in selective processing of sensory inputs.

Keywords: reward, cingulate, salience, decision making, motivation, risk, discounting

INTRODUCTION

Although posterior cingulate cortex (CGp) dysfunction is associated with both Alzheimer's Disease (Minoshima et al., 1997; Hirono et al., 1998; Yoshiura et al., 2002) and schizophrenia (Newell et al., 2006, 2007), the cognitive function of this brain area remains unclear. Neuroimaging studies (Maddock et al., 2003; Buckner and Vincent, 2007; Kable and Glimcher, 2007; Luhmann et al., 2008), lesion studies (Gabriel et al., 1991; Bussey et al., 1996), and neurophysiological studies (McCoy et al., 2003; McCoy and Platt, 2005; Hayden et al., 2008; Pearson et al., 2009) support two distinct functional roles for CGp in decision making.

On one hand, correlations between neural activity and individual decision preferences suggest CGp contributes to decision making by signaling the subjective value of a chosen option (McCoy and Platt, 2005; Kable and Glimcher, 2007; Levy et al., 2011). Indeed, firing rates of neurons in this area track the subjective value of preferred risky options in a choice task (McCoy and Platt, 2005), and BOLD signal correlates with the subjective value of a delayed option in an inter-temporal choice task (Kable and Glimcher, 2007).

However, modulations in neural activity by task engagement, learning, and memory suggest CGp plays a more fundamental role in the allocation of neural resources to cognitive control akin to that of attention in the selective processing of sensory stimuli (Maddock et al., 2001, 2003; Greicius et al., 2004; Luhmann et al., 2008). Firing rates of CGp neurons are modulated by the omission of predicted rewards as well as larger than average rewards (McCoy et al., 2003), signal whether monkeys will switch from a preferred option to a non-preferred one (Hayden et al., 2008), and predict when monkeys will strategically shift from exploiting an option with known value to learning about alternatives (Pearson et al., 2009). Moreover, increased tonic firing rates in CGp predict lapses in task performance (Hayden et al., 2009), corroborating brain imaging studies that have linked high CGp activity to decline in task engagement (Weissman et al., 2006). Finally, CGp lesions in rodents and rabbits impair several forms of associative learning (Gabriel and Sparenborg, 1987; Bussey et al., 1996).

Adjudicating between these two possibilities is difficult because motivational variables associated with cognitive control may covary with valuation (Pearce and Hall, 1980; Maunsell, 2004; Rangel et al., 2008). We tested these two hypotheses by dissociating the subjective value of an option as revealed by choice preference from the degree to which that option differed from a standard, herein defined as decision salience. Monkeys made decisions in three distinct contexts, each offering a choice between options differing in a single relevant variable: risk (McCoy and Platt, 2005), delay to reward (Hwang et al., 2009; Louie and Glimcher, 2010), and the potential to acquire social information at a juice cost (Deaner et al., 2005; Klein et al., 2008). Each variable assumed one of three different levels of decision salience (i.e., risk, delay, or price). We found that, across decision contexts, neuronal activity was uncorrelated with subjective value as estimated from choice frequencies. Instead, firing rates reflected decision salience, the degree of deviance of a chosen option from the standard. Our findings thus argue against the subjective value hypothesis and support the idea that CGp contributes to the motivational allocation of cognitive resources – in part by signaling decision salience.

MATERIALS AND METHODS

Two male rhesus macaques participated in this experiment (monkeys N and S). Monkeys began each trial by fixating on a central square. Following a fixation period (2 s for monkey N, 0.3–2 s for monkey S), they were required to shift gaze to one of two eccentric targets. After a successful gaze shift, a fluid or a fluid plus social reward was delivered (see **Figure 1A**). On each trial, the monkeys

chose between a standard target, offering an immediate, safe, medium-sized reward (200 μL of juice) with no social reward and another, non-standard reward. The identity of this second reward option determined the trial type and varied in blocks. Following reward delivery, an inter-trial interval (ITI) began. The ITI was 5 s in all trials except choices of the delayed option, in which case it was adjusted such that the total trial length for delay trials was approximately the same as all other trials.

Each trial offered one of three possible decision salience levels within three possible trial types. Thus there were nine trial types (see **Figure 1B**). Monkeys completed at least two blocks each (one for each side of the monitor) of the nine trial types within each session. The first trial type gave monkeys a choice between a sure reward and risky gamble on a larger or smaller reward (McCoy and Platt, 2005). We defined risk as the coefficient of variation (CV) in reward value, to permit easy comparison with other studies. While the safe option remained the same across all three levels (200 μL of juice), the risky option could be either high risk (280 μL 50% of the time; 120 μL 50% of the time), medium risk (253 μL of juice 50% of the time; 147 μL of juice 50% of the time), or low risk (227 μL of juice 50% of the time; 173 μL of juice 50% of the time). The second context was a form of a standard delay discounting task (Mazur, 1987; Ainslie and Haslam, 1992; Kim et al., 2008). Monkeys chose between a small, immediately available reward (200 μL of juice – the standard) and a large, delayed reward (233 μL of juice). The delay associated with the large reward could be small (1 s), medium (2 s), or large (3 s), depending on the condition. The final context was a social decision making task based loosely on the "pay-per-view" task described previously (Deaner et al., 2005; Klein et al., 2008), in which monkeys chose between a large amount of juice without an associated picture (200 μL) or a smaller amount of juice paired with a small photograph of a familiar monkey. The amount of juice associated with the picture could be either small (120 μL juice), medium (147 μL of juice), or large (173 μL of juice), depending on the condition. In contrast with previous studies, photographs of different monkeys with different ranks within the colony were randomly interleaved. The safe option (risk context), immediate option (delay context), and non-picture option (social context) were identical, so we refer to this as the standard option. Thus, a standard option was available on every choice, and the identity of the non-standard (outlier) option determined the decision context and level.

Each block consisted of 11 to 21 trials; the specific number was chosen randomly so as to prevent the monkey from guessing when the block would end. Each block contained choices belonging to only one of the nine possible conditions (three levels and three contexts). Each block began with a forced-choice trial in which only the outlier option was available. This trial served to inform the subject about the new block's context and level. In addition, the color of the central fixation square was associated with the decision

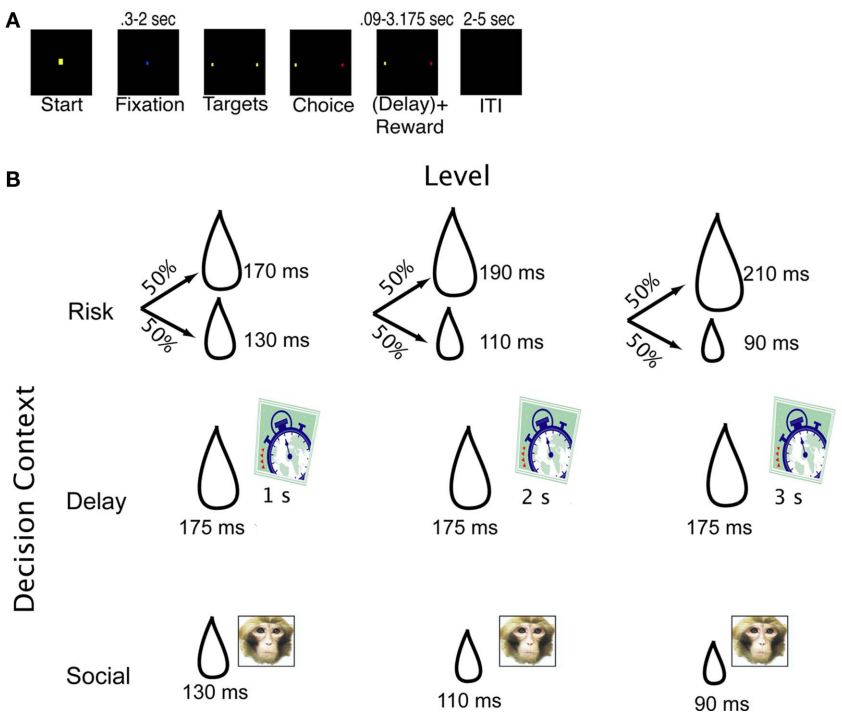

FIGURE 1 | Task design and decision contexts. (A) Trial events. Trials began when a central fixation light appeared. Once the monkeys looked at the fixation light, it changed color to indicate the current context. After a stable fixation period, the fixation light extinguished, and two eccentric yellow dots appeared. When the monkey had shifted gaze to one of these targets, the reward period began. Juice was either delivered immediately, or, in the case of LL choices, after some delay. An adjusting delay followed such that all trials were of approximately the same total length. **(B)** Reward matrix showing outlier outcomes for each level of each context. All recording sessions included blocks composed of one of nine trial types: three conditions (risk, delay, social), each with three levels. Clock indicates delay to reward, the droplet indicates amount of juice delivered, and the picture indicates that a social reward was presented just before juice delivery. The standard option was always 200 μL of juice available immediately, with no picture.

context, so monkeys always had information about whether they were making choices about risk, time, or social/juice reward trade-offs. The standard and outlier options were randomly assigned to the two target locations at the start of each block and remained there for the duration of the block. On the next block of the same type, these assignments reversed. Thus, locations were roughly counterbalanced.

SURGICAL PROCEDURES

All procedures were approved by the Duke University Institutional Animal Care and Use Committee and were designed and conducted in compliance with the Public Health Service's Guide for the Care and Use of Animals. Two male rhesus monkeys (*Macaca mulatta*) served as subjects. A small head-holding prosthesis was implanted in both animals using standard surgical techniques. Six weeks later, animals were habituated to training conditions and trained to perform oculomotor tasks for liquid reward. A second surgical procedure was then performed to place a stainless steel recording chamber (Crist Instruments) over CGp at the intersection of the interaural and midsagittal planes. Animals received analgesics and antibiotics after all surgeries. Throughout both behavioral and physiological recording sessions, the chamber was kept sterile with regular antibiotic washes and sealed with sterile caps.

BEHAVIORAL TECHNIQUES

Monkeys were placed on controlled access to fluid outside of experimental sessions. Horizontal and vertical eye positions were sampled at 1000 Hz by an infrared eye-monitoring camera system (SR Research, Osgoode, ON, USA). Stimuli were controlled by a computer running Matlab (Mathworks, Natick, MA, USA) with Psychtoolbox (Brainard, 1997) and Eyelink Toolbox (Cornelissen et al., 2002). Visual stimuli were small colored squares on a computer monitor placed directly in front of the animal and centered on his eyes. A standard solenoid valve controlled the duration of juice delivery. Monkeys were generally familiar with this type of task, and had performed one of the context types described (risk) previously. Monkeys performed the entire task, consisting of the three contexts, for at least three sessions prior to recording.

MICROELECTRODE RECORDING TECHNIQUES

We recorded action potentials from 71 single neurons in two monkeys (53 in monkey N, 18 in monkey S) during the performance of the task. Single electrodes (Frederick Haer Co.) were lowered under microdrive guidance (Kopf) until the waveform of a single (1–4) neuron(s) was isolated. Individual action potentials were identified by standard criteria and isolated on a Plexon system (Plexon Inc, Dallas, TX, USA). Neurons were selected for recording on the basis of the quality of isolation only, and not on task-related response properties.

We approached CGp through a standard recording grid. CGp was identified using a hand-held digital ultrasound device (Sonosite 180) placed against the recording chamber (Glimcher et al., 2001). We confirmed that we were in CGp using stereotactic measurements, as well as by listening for characteristic sounds of white and gray matter during recording. CGp recordings were made in areas 23 and 31 in the cingulate gyrus and ventral bank of the cingulate sulcus. These recordings were made from areas equivalent to those reported in McCoy et al. (2003), Dean and Platt (2006), Hayden et al. (2008).

ANALYSIS

We used an alpha of 0.05 as a criterion for significance. Peristumulus time histograms (PSTHs) were constructed by aligning spikes to saccade offset, averaging across trials, and smoothing with a 200-ms boxcar. Statistics were performed on binned firing rates, as described for each analysis. To compare firing rates across trials for single neurons, tests were performed on individual trials; to compare firing rates across neurons, tests were performed on average rates for individual neurons. The post-reward epoch was 900 ms, beginning at the completion of reward delivery. The pre-saccadic (pre-choice) epoch was 900 ms, beginning 1300 ms prior to saccade completion. The peri-saccadic epoch was 400 ms, ending at the completion of the saccadic. Analyses were performed using Matlab (Mathworks, Natick, MA, USA).

The main subjective value model was based on a model used in a previous study (Hayden et al., 2007), in which daily choice frequencies were transformed to equivalent juice amounts. The model takes advantage of the roughly linear relationship between choice frequency and juice amount identified in a previous experiment (McCoy et al., 2003). For this study, to reduce day-to-day noise, we added one additional (hypothetical) choice frequency per context (risk: CV of 0; delay: 0 s delay on large reward; social: juice amount equivalent to standard).

RESULTS

MONKEYS EXHIBIT STABLE, ORDERED PREFERENCES IN THREE DECISION CONTEXTS

Each day, monkeys performed a single task with three different embedded decision contexts: risk, delay, and social valuation, each associated with three levels of decision salience. All three contexts required monkeys to shift gaze in order to choose between two eccentric targets associated with different reward properties. In the risk context, monkeys chose between a risky option (50% chance of high reward, 50% chance of low reward) and a safe option (100% chance of medium reward) of equal expected values. We varied decision salience by changing the risk level (CV) of the risky option. In the delay context, monkeys chose between a larger, delayed amount of juice (LL: larger, later) and a smaller amount of juice available immediately (SS: smaller, sooner). Delays could either be 1, 2, or 3 s, depending on the block. In the social valuation context, monkeys chose between a large amount of juice and a small amount of juice paired with a photograph of a familiar monkey (mix of dominant and subordinate males). The photograph option was paired with different small amounts of juice (small, medium, large), depending on the block. The safe, immediate, and non-social options were identical (standard) across the three contexts; only the "outlier" option changed according to block. Thus, the identity of the outlier option determined the decision context. In the risk context, monkeys preferred the probabilistically rewarded option to the safe one (**Figure 2A**), as described previously (McCoy and Platt, 2005; Hayden et al., 2008). In the delay context, monkeys preferred immediate rewards to delayed ones (**Figure 2B**). Finally, in the social context, they preferred larger juice rewards to smaller rewards paired with photographs of familiar monkeys [**Figure 2C**; $p < 0.0001$ in all cases, two-tailed single-sample

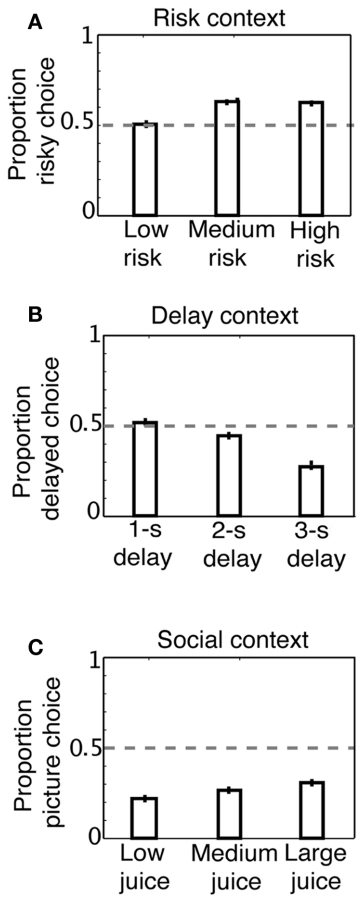

FIGURE 2 | Behavioral preferences used to compute subjective value in the risky, delay, and social contexts. (A) Preferences in risk context. Monkeys significantly preferred a risky reward to a safe reward and had stronger preferences for higher levels of risk. **(B)** Preferences in delay context. Monkeys were significantly delay-averse, preferring smaller, immediate rewards to larger, delayed rewards, and had stronger preferences against longer delays. **(C)** Preferences in social valuation context. Monkeys preferred the standard juice reward to smaller rewards coupled with images, but were more likely to choose to view the image as juice volume was increased.

t-tests; Monkey N risk: $M = 0.59$, SE = 0.008, $t(4247) = 11.5$; delay: $M = 0.42$, SE = 0.008, $t(4310) = -11.3$; social: $M = 0.25$, SE = 0.007, $t(4243) = -37.9$; Monkey S risk: $M = 0.59$, SE = 0.02, $t(708) = 4.8$; delay: $M = 0.41$, SE = 0.02, $t(726) = -4.9$; social: $M = 0.36$, SE = 0.02, $t(745) = -7.8$]. These effects were highly significant for both monkeys.

As noted above, there were three different levels of the outlier option in each decision context (high risk, medium risk, low risk; long delay, medium delay, short delay; large juice, medium juice, small juice), meaning there were nine different possible block types in total (three contexts × three levels). The standard option (no risk, no delay, no picture) was available on all choice trials. We found that preference for the risky option increased with increasing CV in reward [$F(2, 4805) = 31.5$, $p < 0.0001$] as described previously (McCoy and Platt, 2005). As expected (e.g., Myerson and Green, 1995; Reynolds et al., 2002; Freeman et al., 2009), monkeys also chose the smaller, immediate option more often when the delay to the larger option was longer [$F(2, 4877) = 119.8$, $p < 0.0001$]. Finally, as the amount of juice associated with the photograph increased, monkeys were more likely to choose it [$F(2, 4822) = 15.0$, $p < 0.0001$].

NEURONAL FIRING RATES IN CGp DO NOT TRACK BEHAVIORAL PREFERENCES INDEPENDENT OF CONTEXT

We first examined the neuronal response to choice of a risky, delayed, or social option. **Figure 3** shows the firing rates of a single neuron to choice of the outlier option (shown in red) over the standard option (shown in blue). Firing rates were higher for choices of a social or risky option over the standard. **Figure 4** demonstrates that,

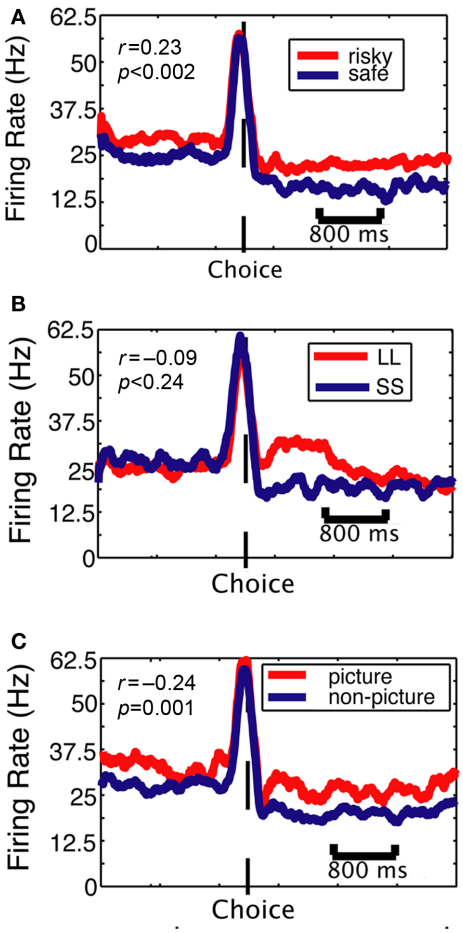

FIGURE 3 | Firing rates of a single CGp neuron are modulated by choice but do not signal value independent of decision context. Plots are aligned to end of choice saccade (dotted line). **(A)** Risk context. PSTH shows average response of population of neurons when monkey chose the risky option (red) or the safe option (blue). **(B)** Delay context. PSTH separated by whether the monkey chose the LL option (red) or the SS option (blue). **(C)** Social valuation context. PSTH separated by whether the monkey chose the picture option (red) or the non-picture option (blue). Pre-choice modulations likely reflect block structure (see main text). Statistics are for correlation between subjective value and firing rate, within context.

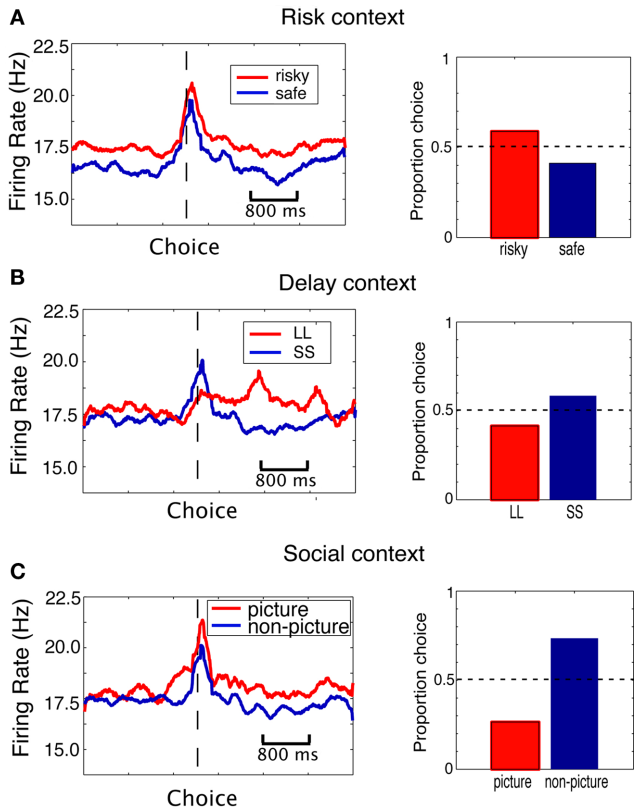

FIGURE 4 | The CGp population response increases when monkeys choose the risky, delayed, and social options – independent of preference. (A) Risk context. Population PSTH separated by whether the monkey chose the risky option (red) or the safe option (blue). On the right is proportion choice of the risky (red) and safe (blue) options. **(B)** Delay context. Population PSTH separated by whether the monkey chose the LL (red) or SS (blue) options. On the right is proportion choice of the LL (red) and SS (blue) options. **(C)** Social valuation context. Population PSTH separated by whether the monkey chose the picture option (red) or non-picture option (blue). On the right is proportion choice of the picture (red) and non-picture (blue) options.

generally, average population activity was stronger when monkeys chose the risky option, which was preferred, but was also stronger when monkeys chose the delayed option and social options, which were not preferred.

We next quantified these effects in our population of studied neurons. During the post-reward epoch (see Materials and Methods), the population as a whole showed higher firing rates during choice of a risky option than during choice of a safe option [$t(70) = 2.39$, $p = 0.02$]. Overall, 19 of the 71 (27%) recorded neurons were significantly modulated by risky versus safe choice; 16 of these showed higher activity when monkeys chose the risky option (see **Table 1**). Of the 19 neurons significantly modulated during the post-reward phase, 11 were also modulated by upcoming choice of the risky option prior to the saccade (10 with higher firing rate for risky option). Seven were modulated during the peri-saccadic period, six of those with higher firing for the risky option. Because both monkeys preferred the risky option, this positive relationship between firing rate and risk replicates previous behavioral and neuronal results

Table 1 | Neurons modulated by choice of the outlier option over the standard option within each task context.

		Risk		Delay		Social/juice	
Post-reward		19		17		14	
Pre-choice	Peri-saccade	11	7	8	5	5	6

Numbers of neurons modulated in the pre-choice and peri-saccadic epochs are out of the number modulated in the post-reward epoch.

(McCoy and Platt, 2005) and is consistent with the hypothesis that CGp firing rates encode the subjective value of a chosen option.

Quantification of data from the other two contexts suggests otherwise. In the delay context, the population showed a higher firing rate when monkeys chose the delayed option than when they chose the immediate option, although this difference was not significant $t(70) = 0.61$, $p > 0.05$. Although the population did not show significantly higher firing rates for one choice over the other, the activity of a substantial minority of neurons (17/71; 24%) was significantly modulated by choices of the larger, later (LL) reward over the smaller, sooner (SS) reward. Although monkeys generally preferred the SS option to the LL, roughly half (nine) of these neurons showed higher activity for choices of the delayed option. Eight of the 17 neurons significant during the post-reward epoch were also significantly modulated during the pre-choice epoch, five of them showing higher firing rates prior to choice of the LL option. Seven of the 17 neurons were significantly modulated during the peri-saccadic epoch, three of them showing higher firing rates during choice of the LL option. Since firing rates were also generally higher when monkeys chose the risky option, this pattern of results is inconsistent with the hypothesis that CGp encodes subjective value.

Finally, the population showed a significantly higher firing rate when monkeys chose the social option over the non-social one [$t(70) = 2.8$, $p < 0.008$], even though the non-social option was strongly preferred. Overall, 14 neurons (20%) were modulated by the choice of the social option over the non-social option. Of these, 11 fired at higher rates when monkeys chose the picture. Five of the 14 were significantly modulated prior to saccade (three with higher firing rates for upcoming choice of the picture option). Six of the 14 were significantly modulated in the peri-saccadic epoch (five with higher firing rates during choice of the picture option). Again, these findings are inconsistent with the idea that CGp signals the subjective value of a chosen option independent of context. **Figure 3** demonstrates that all of these effects can be observed in the activity of a single neuron: this example cell shows higher firing rates during choice of the outlier options relative to the standard, despite contrasting preferences in the three conditions.

CGp NEURONS DO NOT ENCODE SUBJECTIVE VALUE INDEPENDENT OF DECISION CONTEXT

We next quantified the relationship between firing rates of CGp neurons and the subjective value of the chosen option. Subjective value signals in the brain can be identified by correlations between neuronal activity and the preference functions that serve as the basis for estimating value (cf. Montague and Berns, 2002; O'Doherty, 2003; Padoa-Schioppa and Assad, 2006).

We used a measure of subjective value based on revealed preferences that allowed us to assign a value estimate to each option across all decision contexts. Subjective value was estimated using the frequency of choosing the risky, delayed, and social options (outlier options) in each of the nine possible conditions in each session. For each context (risk, delay, social), we fit a line to the day's preference points – one for each level of the non-standard option (low, medium, high risk; short, medium, long delay; small, medium, large juice). In a previous study (McCoy et al., 2003), we gave monkeys (one of whom is also used in this study) choices between different amounts of juice to determine the relationship between reward size and choice frequency. We then used that data to convert choice frequencies to equivalent juice values to model subjective value in the current study (cf. Hayden et al., 2007). For example, a 75% preference for the risky option over the safe one would be equivalent to the frequency with which monkeys choose 220 μL over 200 μL of juice rewarded deterministically. We examined the relationship between our estimate of subjective value and firing rate following delivery of the reward for each neuron, within each context. **Figure 3** shows these relationships for a single neuron. In this example cell, firing rate was positively correlated with subjective value in the risk context, but was negatively correlated with subjective value in the social context.

Overall, during the post-reward epoch the population of CGp neurons was biased toward a positive relationship between firing rates and subjective value in the risk context [$M = 0.066$, $t(70) = 3.5$, $p < 0.001$, **Figure 5A**], biased toward a negative relationship between firing rates and subjective value in the social context [$M = -0.064$, $t(70) = -3.67$, $p < 0.001$, **Figure 5C**], and trended toward a negative relationship between firing rates and subjective value in the delay context [$t(70) = -1.64$, $p = 0.10$, **Figure 5B**]. This sign inversion is contradictory to the hypothesis of subjective value encoding. We also examined the relationship between firing rates and subjective value across all three decision contexts by incorporating all types of trials into our model. When all trials from all contexts and levels were included, there was no relationship between subjective value and firing rate across the population [$t(70) = -1.10$, $p > 0.2$, **Figure 5D**]. We next examined whether these correlation coefficient distributions were not just different from zero, but also from each other. As expected, the risk and delay correlation coefficient distributions were significantly different from each other [$t(70) = 3.72$, $p = 0.0006$] as were the risk and social correlation coefficient distributions [$t(70) = 5.13$, $p < 0.00001$], however, the social and delay correlation coefficient distributions were not significantly different from each other [$t(70) = 1.46$, $p = 0.15$]. If these neurons were encoding subjective value, we would have expected little difference across conditions.

Given that CGp neurons show a weak bias for contralateral choices, we repeated these analyses using the original model for trials that only included contraversive saccades and found the same effects. We found qualitatively similar results to those reported for all saccades, but with significant (negative) encoding in the delay context: Risk, $t(60) = 2.13$, $p = 0.04$; Delay, $t(61) = -2.04$, $p = 0.046$; Social, $t(61) = -2.5$, $p = 0.01$.

In addition to this method, we recalculated our data using an alternative method, in case the particular model of value we chose biased our data against the subjective value hypothesis. Thus, we estimated subjective value using an alternative approach and found highly similar results. We examined whether firing rates matched daily choice frequencies, without any additional transformations. Under this model, both the standard and non-standard options could attain different relative values across different contexts and levels, simply based on different preference levels. Results, however, were similar to other model. In the post-reward epoch, we observed a significant correlation between subjective value and firing rate in the risk context [$t(70) = 2.86$, $p = 0.006$],

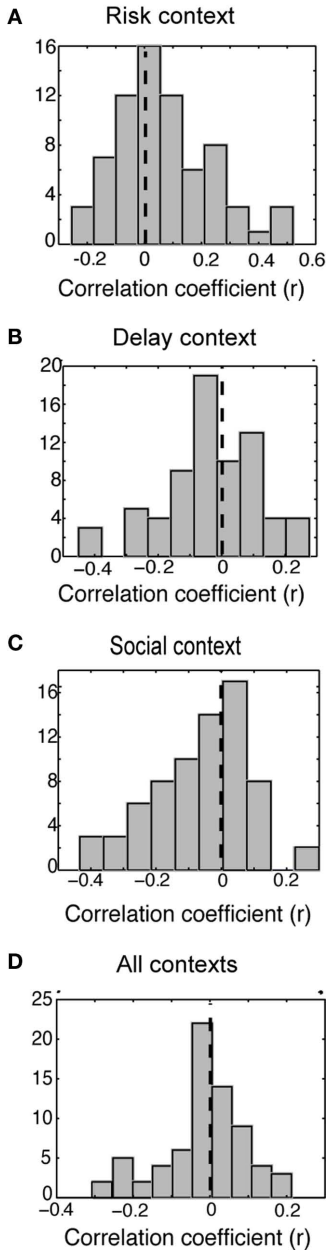

FIGURE 5 |The CGp population does not encode value independent of context. Histogram of correlation coefficients for subjective value (see Materials and Methods) for the: **(A)** Risk context. **(B)** Delay context **(C)** Social valuation context. **(D)** All contexts combined.

a negative correlation in the social context [$t(70) = -3.37$, $p = 0.001$], and a non-significant negative correlation in the delay context [$t(70) = -0.83$, $p = 0.40$].

Thus, although post-reward firing rates varied with which choice the animal made, they were not correlated with subjective value in a consistent fashion across decision contexts.

Given the heterogeneity in response direction amongst CGp neurons, we were concerned that different subsets of neurons may have been activated by one task over another, thus muddling the population results described above. We asked whether the divergent relationships between firing rates and subjective value observed across contexts were the result of separate neuronal populations contributing exclusively to one of the three types of decisions. When we divided cells into positive or negative correlations with subjective value (without regard to significance) in each of the three contexts, we observed the largest number of cells with positive modulation in the risk context, negative modulation in the delay context, and negative modulation in the social context (18/71 cells, see **Table 2**). Furthermore, cells that were significantly modulated in one context were not less likely to be modulated in either of the other contexts than those cells that were non-significant (independent-samples *t*-tests, all $p > 0.1$). For example, neurons that showed an effect of subjective value in the risk context were not less likely to signal value in the delay context than cells that did not signal value in the risk context. This was also true for choice effects (e.g., risky versus safe). Indeed, neurons with higher firing rates for delayed choice over standard (without regard to significance) fired at higher rates for picture choices and risky choices versus the standard option ($p < 0.05$ in both cases). Likewise, neurons with higher firing rates following risky choices also had higher firing rates following picture choices, relative to the standard ($p = 0.03$), and *vice-versa* ($p < 0.02$). Collectively, these results suggest that there are not special populations of neurons that only respond to decisions involving risk, delay, or social information in CGp. Rather, the relationship between firing rates and value, as estimated from revealed preferences, differs depending on context.

FIRING RATES OF CGp NEURONS VARY WITH DECISION SALIENCE

The observed pattern of results – higher activity for choice of a risky, delayed, or social option compared to the standard (certain, immediate, non-social) option – suggest the hypothesis that CGp neurons signal the deviation of the chosen option from an anchor (in this case, the standard option), that is, decision salience, rather than the subjective value of the chosen option. If this were the case we would expect overall higher firing rates for choices of the outlier option than for the standard, regardless of decision context. Combining data across all contexts, outlier choices did yield significantly higher firing rates during the post-reward epoch than standard choices, as expected based on the context-specific results presented above [$t(70) = 2.2$, $p = 0.03$]. Overall, 24 neurons showed significant differences in firing rate after choosing the outlier versus standard options, collapsing across all contexts and levels. Out of these 24 significant cells, 21 showed higher firing rates following choice of the outlier option than following choice of the standard option. This argues strongly for a value-independent decision salience signal.

Furthermore, if CGp neurons encode decision salience this would predict higher firing rates for riskier, later, and smaller juice outlier options, as they are progressively different from the standard. Indeed, neurons responded differently to the various outlier options. We combined data across all contexts and regressed neuronal responses for each cell against outlier level (only outlier choices). We found that regression coefficients were significantly skewed in the positive direction, meaning higher firing rates for more salient options [$t(70) = 3.8$, $p < 0.001$, **Figure 6A**]. Twenty out of 71 cells were significantly modulated by outlier salience (14 in the positive direction). Once again, although these task contexts are quite different, examining them all along the dimension of salience proves useful. This effect was not present in choices of the standard option, either for the post-reward or pre-choice epoch, indicating that this signal does not reflect overall environmental salience. Because the outlier option was also available on these trials, this lack of an effect also argues against processing of available options, and instead ties these signals more closely to choice.

We examined the least and most deviant outlier options from each context in order to more fully quantify this effect (**Figure 6B**). As reported previously (McCoy and Platt, 2005), CGp neurons fired

Table 2 | Number of neurons with firing rates modulated positively and negatively by subjective value, according to decision context.

	D+	D–	
R+	8	9	**S+**
R+	11	18	**S–**
R–	4	7	**S+**
R–	7	7	**S–**

R, risk; D, delay; S, social. "+" indicates a positive relationship between firing rate and value; "–" indicates a negative relationship.

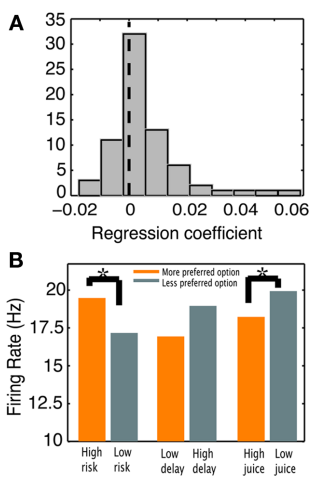

FIGURE 6 | Firing rates of CGp neurons track decision salience. (A) Histogram of regression coefficients for firing rates as a function of choice salience for all neurons in the population. **(B)** Average population response was significantly higher for choosing high risk (versus low risk) and low juice (versus high juice) options. Higher firing rates were associated with options more different from the standard.

at higher rates when monkeys chose the risky option with the highest CV compared with when monkeys chose the risky option with the lowest CV [$t(70) = 3.33$, $p = 0.001$, paired-samples t-test]. In the social context, neurons fired at higher rates during the post-reward epoch when monkeys chose the picture paired with the smallest amount of juice (most different from standard) compared with when monkeys chose the picture paired with the largest amount of juice [$t(68) = -2.41$, $p = 0.019$]. In the case of delayed rewards, firing rates were higher when monkeys chose the 3-s delayed option than when they chose the 1-s delayed option, although this difference was not significant [$t(69) = -1.69$, $p = 0.096$]. However, as clearly evident in the population response (**Figure 4**), firing rates during LL choices were higher during the delay period than prior to the choice, meaning neurons increased their responses during the delay, in anticipation of the reward [$t(70) = 2.5$, $p = 0.015$]. This effect disappears following reward delivery, when firing rates return to pre-choice baselines ($p > 0.9$). Given our other results, this suggests that the delay period itself was the more salient outlying feature in this context. Thus, firing rates were consistently higher when the outlier option deviated more from the standard, strongly suggesting that CGp encodes decision salience rather than the subjective value of a chosen option.

We considered the possibility that these results could be explained by a relatively simple arousal signal. We assessed whether there was a consistent relationship between firing rate and reaction time in this task. Previous studies have showed that, in certain contexts, CGp activity increases with slower reaction times (Hayden et al., 2009), as tonic increases in firing rate in CGp are associated with task disengagement (Raichle et al., 2001). However, here, we did not observe any consistent relationship across cells between firing rate and reaction time (mean correlation coefficient = 0.011, $p = 0.4$), even when only examining significant cells ($p = 0.3$). Moreover, the bias toward higher firing rates during choice of outlier options relative to the standard option was maintained while controlling for reaction times, $t(70) = 3.36$, $p = 0.001$.

DISCUSSION

Our data show that CGp neurons do not signal behavioral preferences consistently across different decision contexts. The population of CGp neurons responded with higher firing rates when monkeys chose the risky option, which was preferred, and the delayed and social options, which were non-preferred. Furthermore, firing rates increased as delay and risk increased, and as amount of juice associated with the social option decreased. These data demonstrate that CGp does not track subjective value in a manner that is independent of the type of decision being made. Instead, CGp neurons appear to encode variables that sometimes covary with preference.

One such variable is what we are calling decision salience: neurons tended to fire at higher rates when the chosen option was more aberrant from the standard option available on every trial. This type of outlier encoding may be useful for guiding learning and memory (Pearce and Hall, 1980), a function previously linked to CGp (Cabeza and Nyberg, 2000; Maddock et al., 2003; McCoy et al., 2003).

We have operationally defined decision salience purely in the context of choosing outcomes that deviate from a standard option. Unfortunately, the task we used was not designed to examine learning, but rather to examine preference signals across distinct decision contexts, although these signals would certainly be useful for learning about unusual events. That being said, we do not think this signal fits with simple cue processing for associative learning. Instead, these signals seem to track the salience of the *chosen* option. One way to examine this is to compare trials on which the monkey chose the standard option even though the outlier option was also available. If this signal reflects broader option or cue processing, then the neural signal should track salience regardless of option chosen. Instead, firing rates when the standard option was chosen do not vary based on the salience of the outlier option. Thus, although we believe these signals to be useful for learning, at this point we remain agnostic as to the details of this process.

Our lab previously showed that firing rates of neurons within CGp predict preferences for chosen options in a risky choice task similar to the one used here (McCoy and Platt, 2005). The present study replicates those previous results. By contrast, our finding that the CGp population tends to respond more strongly when monkeys choose the delayed but non-preferred option conflicts with a recent fMRI paper which found that hemodynamic responses in human CGp vary with subjective value in a delay discounting task (Kable and Glimcher, 2007; Levy et al., 2011). The discrepancy between the present study and these earlier findings may reflect species differences in neuronal processing, differences in task design (i.e., the use of primary versus monetary rewards), or discontinuities between the BOLD signal and single unit firing (Logothetis et al., 2001). Other studies have suggested the BOLD signal in CGp is stronger during decisions concerning delay than risk (Weber and Huettel, 2008). Furthermore, Luhmann et al. (2008) reported in a recent paper that activation of human CGp increased with choice of a delayed reward – an effect we confirmed on the level of the single neuron. They hypothesized that such signals may be linked to self-projected time rather than decision processing. Firing rate modulations observed here, however, suggest that CGp activation may not indicate self-projection specifically, but may instead reflect neural processing involved in tracking salience.

Overall, our findings suggest that CGp signals decision salience or even uncertainty more broadly (Critchley et al., 2001; Behrens et al., 2007). The consistently higher firing rates we observed for the "outlier" options (risky, delayed, social) may signal deviation from standard or predicted outcomes, a variable important in attentional models of learning (Mackintosh, 1975; Pearce and Hall, 1980). Such a signal would indicate when and how rapidly learning or behavioral adjustment would occur, but would not provide information about precisely what should be learned. Consistent with this idea, a previous study found that firing rates of CGp neurons were higher when monkeys explored their options than when they pursued a single source of reward (Pearson et al., 2009), a pattern consistent with the idea that CGp neurons signal decision salience. With prominent connections to the medial temporal lobes, CGp is well-positioned anatomically to provide an instructional signal to engage learning.

ACKNOWLEDGMENTS

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Rodent versions of the Iowa gambling task: opportunities and challenges for the understanding of decision-making

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Impaired decision-making is a core problem in several psychiatric disorders including attention-deficit/hyperactivity disorder, schizophrenia, obsessive–compulsive disorder, mania, drug addiction, eating disorders, and substance abuse as well as in chronic pain. To ensure progress in the understanding of the neuropathophysiology of these disorders, animal models with good construct and predictive validity are indispensable. Many human studies aimed at measuring decision-making capacities use the Iowa gambling task (IGT), a task designed to model everyday life choices through a conflict between immediate gratification and long-term outcomes. Recently, new rodent models based on the same principle have been developed to investigate the neurobiological mechanisms underlying IGT-like decision-making on behavioral, neural, and pharmacological levels. The comparative strengths, as well as the similarities and differences between these paradigms are discussed. The contribution of these models to elucidate the neurobehavioral factors that lead to poor decision-making and to the development of better treatments for psychiatric illness is considered, along with important future directions and potential limitations.

Keywords: Iowa gambling task, animal model, validity, dopamine, serotonin, neurobiology

INTRODUCTION

Decision-making plays a pivotal role in daily life. Impairment in this process, as observed in several psychiatric disorders, results in an inability to make profitable long-term decisions that incorporate expectations of future outcomes (for review, see Dunn et al., 2006). Impaired decision-making is recognized as a core problem in disorders like substance abuse (Grant et al., 2000; Bechara, 2001; Bechara and Damasio, 2002; Bechara et al., 2002; Ernst et al., 2003; Bechara and Martin, 2004; Whitlow et al., 2004; Dom et al., 2006; Hanson et al., 2008), pathological gambling (Cavedini et al., 2002b; Brand et al., 2005; Goudriaan et al., 2005, 2006), schizophrenia (Bark et al., 2005; Shurman et al., 2005; Kester et al., 2006; Lee et al., 2007b; Sevy et al., 2007), obsessive–compulsive disorder (OCD; Lawrence et al., 2006; da Rocha et al., 2008; Cavedini et al., 2010; Starcke et al., 2010), eating disorders (Cavedini et al., 2004; Tchanturia et al., 2007; Liao et al., 2009; Brogan et al., 2010), attention-deficit hyperactivity disorder (ADHD; Toplak et al., 2005; Garon et al., 2006; Malloy-Diniz et al., 2007; Luman et al., 2008) chronic pain (Apkarian et al., 2004; Verdejo-García et al., 2009), and Parkinson's disease (Brand et al., 2004). Therefore, understanding the mechanisms underlying poor decision-making is key to successful treatment of neurological and psychiatric disorders. This is why decision-making is studied intensively by disciplines ranging from neuroscience, cognitive and social psychology, to experimental and behavioral economics (Kahneman and Tversky, 1979) leading to the recent interdisciplinary field of neuroeconomics that combines all these disciplines (Glimcher et al., 2009).

The Iowa gambling task (IGT) is the most commonly used task to assess decision-making performance in a clinical setting (Bechara et al., 1994, 1999). The IGT is particularly interesting because it mimics the complexity of the choices that we are confronted with in everyday life. Its design incorporates the unpredictability of the consequences of a choice, the need to weigh short- and long-term gains and losses, and the necessity to exert behavioral control to maximize gains in the long-term. Successful performance requires the integration of several executive functions: individuals must demonstrate flexibility in planning to account for various outcomes, constantly monitor incoming information, evaluate the risk–reward ratio for various decision-making options, and refrain from choosing the options that are immediately more rewarding. For these reasons, successful performance requires the integration of several executive functions. The IGT was originally developed to assess the specific cognitive impairments of prefrontal cortex-damaged individuals (Bechara et al., 1994), but impaired performance has subsequently been observed following damage to other brain regions such as the amygdala, insula, and more controversially, the dorsolateral prefrontal cortex (dlPFC) (Bechara et al., 1998, 1999; Manes et al., 2002; Clark et al., 2003; Fellows and Farah, 2005), as well as in a range of psychiatric

populations (see above). Several (psychiatric) conditions induce various kinds of deficits in the IGT, like disadvantageous deck preference (schizophrenia, OCD, pathological gambling, substance abusing individuals, psychopathic individuals, ADHD, chronic pain) with preference for infrequent punishments (ADHD, schizophrenia); no preference [anxiety, (Miu et al., 2008; de Visser et al., 2010)]; slower learning (mania, substance-dependent individuals) or deficits in reversal learning (schizophrenia; for review, see Dunn et al., 2006). The effects of genetic polymorphisms, pharmacological treatments, as well as functional neuroimaging data, have significantly expanded our knowledge of the neural substrates underlying decision-making, and how their functions are compromised in individuals with decision-making deficits.

Interest is growing in the development of rodent models of decision-making for several practical reasons (see also Potenza, 2009). First, such models are indispensable for the dissection of precise mechanisms involved in decision-making, such as the role of specific brain regions and circuits, modulation by the monoaminergic systems, and neurodevelopmental events. Second, rodents are particularly suitable for screening and identifying risk or protective factors for poor decision-making. Rodent studies are not subject to the same time constraints associated with longitudinal studies in human populations and easily allow the study of inter-individual differences in behavioral and cognitive capacities (Rivalan et al., 2009b). Third, animal models are particularly valuable since environmental conditions as well as genetic variation can be carefully controlled. As such, animal models of the IGT have recently been developed (van den Bos et al., 2006; Pais-Vieira et al., 2007; Rivalan et al., 2009a; Zeeb et al., 2009). These models are largely complementary, yet have distinct strengths. Here we aim at describing the current state of these novel models with respect to face, predictive, and construct validities. We will present recent findings that demonstrate their potential to investigate the neuropsychobiological mechanisms of decision-making as well as directions for future research.

THE IOWA GAMBLING TASK

TASK CHARACTERISTICS

The IGT requires individuals to choose cards, one by one, between four different decks to earn money. Two decks are equally advantageous in the long run because cards chosen from these decks provide immediate moderate monetary gains but also moderate or low *losses* according to two different probability schedules. Two decks are equally disadvantageous in the long run because even though immediate gains are higher, the unpredictable losses are also higher, according to two different probability schedules (**Figure 1**). Thus, a conflict is induced between immediate high rewards and long-term gains. Participants are not provided with any information as to which choice is optimal, but they are instructed to try to maximize their gains as much as possible by freely choosing cards from each deck, and have the ability to switch between decks at any time (Bechara et al., 1999). Subjects therefore need to discover the task contingencies by trial and error. This sets the IGT apart from tasks that overtly signal the odds of winning such as the Cambridge Gambling Task (Clark et al., 2003).

When performing the IGT, healthy human subjects usually display a shift from primarily explorative behavior at the beginning of the task, during which they sample from all decks, toward a more exploitative strategy involving substantially more choices of the advantageous options associated with the best long-term outcome (Bechara et al., 1994, 1999; Brand et al., 2007b). Thus, decision-making is first made under ambiguous conditions, in that the subjects do not know what the reinforcement contingencies are. Following repeated sampling from the decks, it can be assumed that subjects are more aware of the chances of winning or losing associated with each deck, and therefore risky decision-making can take place (Stoltenberg and Vandever, 2010, but see Fellows and Farah, 2005).

Patients suffering from psychiatric disorders in which decision-making is compromised typically persevere in their choice of the disadvantageous options that yield immediate large rewards, despite larger losses in the long-term. Interestingly, a subset of healthy individuals also makes poor decisions in the IGT, suggesting a continuum between normal and pathological conditions (Brown and Barlow, 2005). Therefore, it can be hypothesized that poor decision-making in clinical and non-clinical populations shares common neuropsychological characteristics. As such, identification of these markers could improve our understanding of the transition from a healthy vulnerable state to psychiatric conditions.

NEURAL SUBSTRATES

Studies using brain-lesioned patients and imaging techniques have provided consistent evidence that decision-making depends on

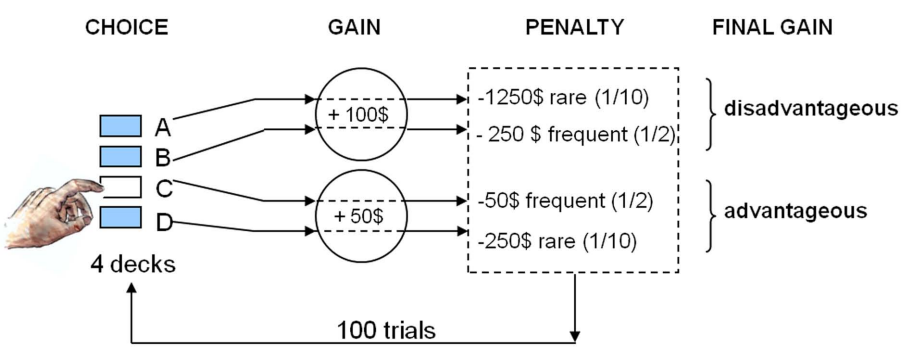

FIGURE 1 | Schematic set-up of the Iowa gambling task.

the integrity of, and functional connectivity between, many brain areas. The main structures are the amygdala, the insula, the striatum (STR), and several frontal cortical regions, including ventromedial prefrontal cortex (vmPFC), orbitofrontal cortex (OFC), the anterior cingulate cortex (ACC), and dlPFC (Bechara et al., 1999; Manes et al., 2002; Bolla et al., 2004; Tucker et al., 2004; Fellows and Farah, 2005; Hsu et al., 2005; Brand et al., 2007a).

The somatic marker hypothesis proposes that emotion-based biasing signals arising from the body are integrated in higher brain regions, notably the vmPFC, the amygdala, the insula, and the somatosensory cortex to regulate complex decision-making (Bechara et al., 1997; Dunn et al., 2006). This hypothesis is based on the fact that successful IGT performance is related to the development of somatic marker signals, as indexed by the magnitude of anticipatory skin conductance responses, before any conscious knowledge of the adapted choices (Bechara et al., 1994, 1997). These signals serve as an indicator of the value presented. If they are ineffective, like in vmPFC lesioned people, solving the task is no more possible. Within the vmPFC, the OFC is involved in the treatment, evaluation and filtering of perceptual, social, and emotional information (Elliott et al., 2000). This region is strongly interconnected with areas within the limbic system, particularly the basolateral amygdala (BLA), and receives prominent inputs from sensory association cortices. This pattern of connectivity suggests that the OFC plays a role in integrating potentially salient information about environmental contingencies (Ongur and Price, 2000), and uses this information to assign a value to a reward and signal outcome expectancies which can thus influence action selection (Schoenbaum et al., 2003; Rolls and Grabenhorst, 2008; Mainen and Kepecs, 2009; Takahashi et al., 2009). Thus, the OFC allows the representation of the reinforcing consequences of a choice to adapt goal-directed behaviors (Mainen and Kepecs, 2009) and modulates this value according to the contingency changes (Schoenbaum et al., 1998; Murray et al., 2007; Hayton and Olmstead, 2009).

The ACC is a converging area for cognitive and motor commands (Paus et al., 1993) that monitors and detects the presence of conflicts related to actions (Magno et al., 2006; Oliveira et al., 2007), whereas the dlPFC, tightly connected with ACC and OFC (Barbas, 2000), engages a top-down process required to monitor and implement change (Hyafil et al., 2009). The ACC signals error-likelihood (Sallet et al., 2007) and has a key role in choosing and updating appropriate actions when the environment is uncertain or dynamic (Kennerley et al., 2006; Quilodran et al., 2008), and in combining information about the costs and benefits associated with alternative actions (Rudebeck et al., 2006). This update is made in combination with the dlPFC, which is critically involved in the temporary maintenance of recently acquired information (Lee et al., 2007a), and in the detection of action–outcome contingencies (Balleine and O'Doherty, 2010), a major aspect of associative learning that allows the elaboration of goal-directed responding.

It has been suggested that the exploration and exploitation phases of the IGT involve different brain areas (van den Bos et al., 2007). The exploration phase may be mediated by the amygdala and ventral STR and their projections to the OFC (Bechara et al., 1999; Knutson et al., 2001). When the task progresses and a preference for the advantageous decks is emerging, the ACC, dlPFC, and dorsal STR may be recruited to engage in cognitive control of the once established choice in order to maintain and exploit this strategy to secure long-term payoff (Bush et al., 2000; Ernst et al., 2002; McClure et al., 2004; Ridderinkhof et al., 2004; Pezawas et al., 2005). However, large inter-individual differences in brain areas recruitment according to performances in the IGT, certainly occurs. Animal models of the IGT are uniquely placed to assess the validity of these theories, as brain imaging studies or lesions to particular areas can be selectively implemented at different stages of training, thereby preferentially targeting either the exploitation or exploration phases (de Visser et al., 2011b; Rivalan et al., 2011; Zeeb and Winstanley, 2011).

NEUROMODULATORS

The dopaminergic and serotonergic systems, known to facilitate functional connectivity between the limbic and cortical regions, are important candidates for modulating decision-making. Changes in the functioning of these neurotransmitter systems have been associated with pathological gambling, the psychiatric disorder perhaps best classified as a disorder of excessive risk-taking behavior and maladaptive decision-making (Shinohara et al., 1999; Seedat et al., 2000; Meyer et al., 2004; Pallanti et al., 2006; Zack and Poulos, 2007; Marazziti et al., 2008; Pattij and Vanderschuren, 2008). Furthermore, several polymorphisms in serotonergic and dopaminergic genes have been identified that affect frontal and sub-cortical brain function and personality traits (e.g., neuroticism, harm avoidance, persistence, and novelty-seeking), which play a central role in decision-making (e.g., Ha et al., 2009; Krugel et al., 2009; Homberg and Lesch, 2010; Juhasz et al., 2010; Paloyelis et al., 2010).

Serotonergic system and decision-making in the IGT

Several lines of evidence suggest that there is an inverse relationship between serotonin levels and impulsivity (Linnoila et al., 1983; Soubrie, 1986), a trait that may affect decision-making. For instance, users of the serotonergic neurotoxic drug MDMA show poorer IGT performance and elevated self-reported impulsivity relative to controls (Hanson et al., 2008). Additionally, in OCD patients, chronic treatment with risperidone, a mixed 5-HT_{2A}-D_2 receptor antagonist, was found to improve overall IGT performance in patients exhibiting initially worse performance (Cavedini et al., 2002a).

Gene variants related to serotonin function have been associated with deficits in decision-making during the IGT. In particular, variants in the ACGCCG haplotype of the tryptophan hydroxylase (TPH)-1 gene (Maurex et al., 2009), polymorphisms in the serotonin-related TPH-2 and monoamine oxidase A (MAOA) genes (Jollant et al., 2007) and in the common serotonin transporter (SERT) promoter (Lesch et al., 1996) have been linked to poor IGT performance. Furthermore, patients with major depression or OCD carrying the low activity (short; s) allelic variant of the serotonin-transporter-linked polymorphic region (5-HTTLPR) showed increased choice of the disadvantageous options in the IGT (Must et al., 2007; da Rocha et al., 2008; He et al., 2010; Stoltenberg and Vandever, 2010). Comparable results were obtained in healthy female subjects (Homberg et al., 2008; van den Bos et al., 2009b, but see Lage et al., 2011). However, studies based on male volunteers

have yielded conflicting results (He et al., 2010; Stoltenberg and Vandever, 2010; Lage et al., 2011). Because the SERT is responsible for serotonin reuptake into the presynaptic nerve terminal, the s-allele is hypothesized to be associated with increased extracellular serotonin levels (Lesch et al., 1996; Kalueff et al., 2009). Of interest, the s-allele, compared to the l-allele, is associated with amygdala hyperactivity in response to fearful stimuli and at rest (Hariri et al., 2002; Canli et al., 2006). This hyperactivation correlates with reduced volume of the ACC, as well as a functional and anatomical uncoupling between the ACC and amygdala (Pezawas et al., 2005; Pacheco et al., 2009) and hyperactivity of the vmPFC (Heinz et al., 2005). One speculation is that people carrying the 5-HTTLPR s-allele are hypervigilant, which is advantageous when environmental stimuli are controllable and manageable. Indeed, in a risky decision-making task with choice probability outcomes made explicitly s/s subjects chose more advantageously due to increased risk adversity (Kuhnen and Chiao, 2009). Conversely, under conditions in which stimuli are uncertain, such as during the IGT, s-allele carriers engage in maladaptive behavior (Homberg and Lesch, 2010). Overall, these data indicate that serotonin signaling can negatively affect decision-making on the IGT, with possible sex-dependent effects during the explorative phase of the task.

Dopaminergic system and decision-making in the IGT

Changes in the dopaminergic system have likewise been shown to modulate IGT performance. As previously noted, poor IGT performance has been observed in several pathologies related to dopamine dysfunction, such as schizophrenia, Parkinson's disease, drug addiction, and pathological gambling (Comings et al., 1996; Rogers et al., 1999; Mimura et al., 2006). Dopamine is critically involved in associative learning (Schultz, 2002) time perception (Meck, 2006) and signaling within the reward system (Di Chiara and Bassareo, 2007), all of which are fundamental processes required for decision-making. Consequently, it is not surprising that reduction of dopaminergic levels impairs decision-making in healthy individuals. Acute administration of a branched-chain amino acids (BCAA) mixture lowers the plasma ratio of dopamine's precursor amino acids and decreases dopaminergic activity (Harmer et al., 2001; Gijsman et al., 2002). This treatment also orientates healthy male participants toward disadvantageous decks in later trials as their dopamine levels reduce, thus indicating a fundamental function of dopaminergic signaling in advantageously guiding decision-making during the IGT (Sevy et al., 2006). This impairment could be related to reduced perception of probability and time, given that attention was shifted toward more recent events compared to more distant events (van den Bos et al., 2007). PET imaging data also indicate a positive correlation between dopamine release in the ventral striatum and IGT performance in healthy male participants (Linnet et al., 2010), yet a negative correlation in problem gamblers (Linnet et al., 2011). However, the D_2 antagonist haloperidol increased the drive to play slot machines in pathological gamblers, but not in healthy controls (Zack and Poulos, 2007).

Two genetic factors mediating dopamine signaling, namely the catechol-*O*-methyltransferase (COMT) enzyme and the D_4 dopamine receptor (DRD_4), are also related to IGT performance. The rs4818 C/G polymorphism of the COMT gene, which results in an 18-fold divergence of enzymatic activity between the high activity variant (G allele) and low activity variant (C allele; Nackley et al., 2006), has been shown to significantly affect performance in the IGT. In particular, male subjects homozygous for the high activity variant performed better than those carrying the low activity variant (Roussos et al., 2008). In a financial risk decision-making task in which subjects were informed on the payoff of choice options carriers of the 7-repeat allele of DRD_4 were significantly more risk seeking relative to those individuals without the 7-repeat allele (Kuhnen and Chiao, 2009), indicating that the 7R allele is associated with novelty-seeking regardless of choice conditions (uncertain or certain). Another COMT gene polymorphism, Val158Met, is associated with IGT performance in healthy females. The Met/Met variant, related to lower COMT activity and higher constitutive dopamine prefrontal cortical levels, lead to poorer performances compared to Val/Val (Lotta et al., 1995; Mannisto and Kaakkola, 1999; Chen et al., 2004; van den Bos et al., 2009b); but see (Kang et al., 2010). Interestingly, carriers of both the Met/Met and 5-HTTLPR-s/s genotypes displayed the worst IGT performance among all possible COMT and 5-HTTLPR genotype combinations (van den Bos et al., 2009b), indicating that the dopaminergic and serotonergic systems may interact in the modulation of IGT choice behavior.

Regarding the variable number of tandem repeat (VNTR) polymorphism in the DRD_4 gene, healthy male carriers of the seven repeats (7R) allele of this gene choose significantly more cards from disadvantageous decks in the IGT compared to participants exhibiting the 4R allele (Roussos et al., 2009). This 7R allele is associated with lower transcriptional/translational levels and diminished *in vivo* receptor responsivity compared to the four repeats (4R) allele (Hutchison et al., 2003; Hamarman et al., 2004; McGough, 2005; Brody et al., 2006; Ebstein, 2006).

Collectively, these data suggest that dopamine, possibly in interaction with serotonin, can modulate decision-making as measured in the IGT. Serotonin may be inversely associated with IGT performance, whereas directional consensus for dopamine is not yet fully clear. Pathological gamblers and healthy controls appear to react differently to dopaminergic manipulations, and may also differ in their baseline and gambling-induced changes in DA release. However, our understanding of the monoaminergic modulation of IGT performance is still limited, and consequently, pharmacogenetic treatment of decision-making deficits in patients is currently a distant goal.

MODELING THE IGT IN RODENTS

It is comparatively easy to perform pharmacological, genetic, and environmental manipulations in mice and rats. Hence, rodent IGT models (*RGTs*) can make a crucial contribution to scientific and medical advances in the field of decision-making. For this purpose, paradigms which capture the essence of the IGT have been developed for use in rodents in order to establish animal models of human decision-making with high face and construct validities.

The IGT (Bechara et al., 1994) has several key features that had to be reproduced. As reviewed below, four different types of rodent IGT models have been designed that incorporate several of these key features (**Table 1**). These models differ both in the equipment used (mazes vs. operant chambers), the task duration (from a single session to several daily sessions), the learning of task contingencies and the ratio between advantageous vs. disadvantageous

Table 1 | Main features of the human and rodent gambling tasks.

Task features	IGT	$RGT_{reward\ or\ quinine}$	$RGT_{reward\ probabilities}$	$RGT_{one\ session\ reward\ and\ time\text{-}out}$	$RGT_{reward\ or\ time\text{-}out}$
Original references	Bechara et al. (1994)	van den Bos et al. (2006)	Pais-Vieira et al. (2007)	Rivalan et al. (2009)	Zeeb et al. (2009)
Apparatus	Computerized card game	Manually operated maze	Manually/automated arena	Automated operant chamber	Automated operant chamber
No. of choice options	4	4	2	4	4
Reward	Monetary gain	Sucrose pellets	Sucrose pellets	Palatable food pellets	Sucrose pellets
Reward occurence	Each trial	Alternate with punishment	Alternate with punishment	Each trial	Alternate with punishment
Punishment	Monetary loss	Quinine pellets	No reward	Time-outs	Time-outs
Conflict immediate rewards	100 (A and B) vs. 50 (C and D)	3 (A) vs. 1 (B)	3 (A) vs. 1 (B)	2 (A and B) vs. 1 (C and D)	3;4 (A and B) vs. 1;2 (C and D)
Conflict long-term payoff	Per 10 cards −250 vs. +250	Per 10 trials 3 vs. 8 pellets ratio = 2.7	Per 10 trials 9 vs. 8 pellets ratio = 0.9	Total test: 60 vs. 300 pellets ratio = 5	Total test: 353 vs. 117 (average) ratio = 3
Task duration	Single session (100 trials)	10 daily sessions (10–20 trials)	Single session	Single session (1 h)	25 daily sessions for stability (approximately 100 trials per 30 min session)
Pre-training procedure	None	10-min habituation	20–25 days	5–7 days	10–15 days incl. 7 forced-choice sessions
Prior knowledge of contingencies	No	No	No	No	Yes
Motivational aspects	n/a	90–95% of FFW	80% of FFW	95% of FFW	85% of FFW

Values for the conflict long-term payoff are hypothetical calculations for $RGT_{one\ session\ reward\ or\ time\text{-}out}$ and $RGT_{reward\ and\ time\text{-}out}$ (based on a fixed trial duration of 9 or 5 s, respectively). FFW, free-feeding weight.

options. The way in which loss is signaled also differs: making sugar pellets aversive through the addition of the bitter-tasting substance quinine (van den Bos et al., 2006; rats and mice), simple non-reward (Pais-Vieira et al., 2007; rats), or the delivery of time-out periods on loss trials which minimize the number of pellets the animals can earn (Rivalan et al., 2009a; rats, Zeeb et al., 2009; rats, Young et al., 2011; mice).

CONFLICT BETWEEN PROBABILITIES OF HIGH FOOD REWARD VS. QUININE: A FOUR-ARM BOX MAZE MODEL ($RGT_{REWARD\ OR\ QUININE}$)

The first experimental protocol aiming to reproduce the characteristics of the IGT in rodents was developed by van den Bos et al. (2006). This task measures the choice between four goal arms, two of them containing either food rewards or punishments per choice. High amount of rewards is combined with the incurrence of a high amount of punishment in the disadvantageous arm, as opposed to the advantageous one. Uncertainty is given by varying the sequence of sugar or quinine pellet presentation. The apparatus (**Figure 2**) consists of a box divided in three different areas: a starting zone, a choice zone, and an arena divided in four parallel arms. The goal arms, labeled A, B, C, and D, are provided with internal visual cues (symbols of different shapes and colors) to help animals in differentiating them during the task apart from the spatial location. They contain "monetary rewards" in the form of sugar pellets, or "monetary punishments" that are quinine-treated (bitter) sugar pellets. Before testing, animals are habituated to the sugar pellet taste and briefly allowed to explore the maze (10 min). Any animals which continue to eat the quinine-treated sugar pellets are removed from the experiment. Test trials are initiated by removing the slide door from the start box. The animal is allowed to freely explore the choice area. A choice for one of the arms is made when the animal has walked into the arm for at least one-third of the length of the arm. Once a choice is made, the arm is closed to prevent the animal from walking back without investigating the reward cup. During testing [10 trials a day for 12 days, but modifications of this schedule have been used (de Visser et al., 2011b)], the pre-arranged schedule of wins and losses associated with the arms are represented according to a pre-arranged random order of sugar and quinine pellets for each arm of the box. One "disadvantageous" and one "advantageous" arm are present. In the former case, the chance of obtaining high immediate rewards combined with the incurrence of a high net loss in the long run is reproduced by presenting three sugar pellets once every 10 choices and one quinine-treated pellet every other time. In the latter case, the possibility of receiving low immediate rewards but having a net gain over multiple choices is achieved by administering one sugar pellet eight times in 10 selections and one quinine-treated pellet every other time. The

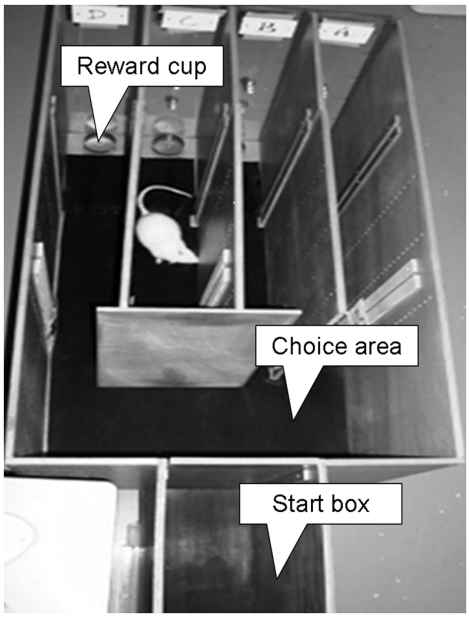

FIGURE 2 | The four-arm box maze model ($RGT_{reward\ or\ quinine}$): top view of the maze with start box, choice area, and four arms with reward cups. When an animal has made a choice for a particular arm, this arm is closed off with a slide to prevent the animal from returning to the choice area before investigation of the reward cup.

uncertainty of rewards and punishments per choice provided by the human task is maintained by varying the sequence of sugar or quinine pellet presentation between blocks of 10 trials in each arm. Consequently, the net gain ratio between advantageous and disadvantageous options is 2.67. The distribution of punishments is randomized per 10 trials and disadvantageous options are not "stacked" toward the end of the task (see Fellows and Farah, 2005). Control for non-specific exploration is assessed by entries into the two empty arms. A mouse version of the IGT has also been designed by van den Bos et al. (2006), using an eight-arm radial maze. This task presents main characteristics that similar to those of the rat gambling task as described above.

Recently, an operant version of $RGT_{reward\ or\ quinine}$ has been developed using specially designed operant panels that are placed in the home cage of rats (Koot et al., 2009, 2010). Next to measuring decision-making, this task allows assessment of impulsivity (Koot et al., 2010) and is currently being further validated.

PREFERENCE FOR HIGH VS. LOW PROBABILITIES TO GET SIMILAR AMOUNT OF REWARD: A TWO-LEVER OPERANT CHAMBER MODEL ($RGT_{REWARD\ PROBABILITIES}$)

In 2007, a second rodent task that modeled some features of the IGT was established by Pais-Vieira et al. (2007). This task measures the preference for an infrequent high amount of food compared to a more frequent, lower amount of food, both options leading to an almost similar amount of total reward. Another task was recently established, based on the same principle (Roitman and Roitman, 2010), but with a lower level of unpredictability.

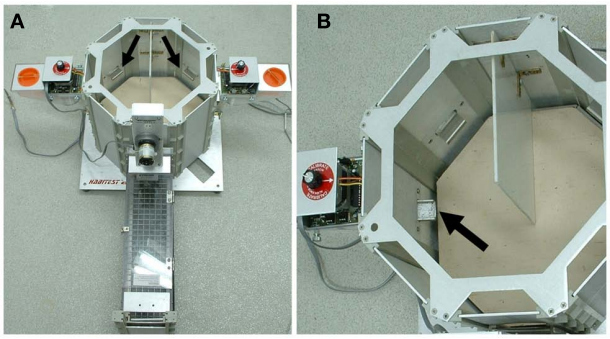

FIGURE 3 | The two-lever operant chamber model ($RGT_{reward\ probabilities}$). **(A)** Octagonal arena connected to a starting corridor. Levels are indicated by the arrows. **(B)** The arena is divided in two sides by a central separator, each containing one lever and one food cup (indicated by an arrow) connected to an automated pellet dispenser.

The apparatus (**Figure 3**) consists of an octagonal arena connected to a starting corridor through a guillotine door. The arena is divided in a right and a left side by a central separator, and each half of the arena is provided with one food cup and one lever connected to an automated pellet dispenser. Training consists of two phases: first, animals undergo a series of sessions to get familiarized with the testing apparatus and to learn the association between lever presses and food delivery. Subsequently, rodents are subjected to five sessions of 30–90 trials in which the outcome values are identical for both sides of the arena (one food pellet in 8 out of every 10 consecutive presses). These sessions serve as a control for individual spatial bias: animals preferring one side of the arena in more than 70% of the trials in two of the five sessions are removed from the study. Each trial begins with the animal in the starting corridor; upon lifting of the guillotine door the animal chooses between going to the left or the right side of the arena and presses the corresponding lever. Lever pressing results in either the delivery of chocolate flavored sucrose pellets or no food delivery. Subsequent presses of the levers have no effect (retractable levers have also been used without any change in task performance). Each trial lasts 20 s after which the animal is hand-removed from the arena and placed back in the closed starting corridor. Then, a new trial will start after a variable inter-trial interval (ITI) of 5–10 s to prevent behavioral adjustment to the session limit. Trials in which the animal fails to press a lever within the 20-s are counted as "incomplete."

Final $RGT_{reward\ probabilities}$ testing consists of a single probe session of 90 trials. Reward contingencies associated with the levers are set so that one leads to frequent small rewards and the other to infrequent large rewards. Both levers have non-rewarded trials and both lead to similar long-term gains in a pseudo-random order, levers being counterbalanced between animals. Options are not "stacked" to favor reward delivery at the beginning of the session (see Fellows and Farah, 2005). During this test session, one lever remains at the reward settings of the training (one food pellet in 8 out of every 10 consecutive presses) while the other lever is set for rewarding three food pellets in 3 out of every 10 consecutive presses. The maximum gain of pellets per 10 trials is comparable

for the low and high risk levers [8 vs. 9; but an equal maximum gain of nine pellets for both levers does not change task performance (Ji et al., 2010)]. As in the human IGT, control animals display a preference for the lever with infrequent large rewards in the beginning of the session, but shift their preference to the lever with frequent small rewards in the second half of the test.

ONE SESSION CHOICE FOR HIGH REWARD/IMPROBABLE LONG PENALTIES VS. LOW REWARD/IMPROBABLE SHORT PENALTIES: THE FOUR-HOLE OPERANT CHAMBER MODEL ($RGT_{\text{ONE SESSION REWARD AND TIME-OUT}}$)

Rivalan et al. (2009a) recently proposed an alternative automated rodent IGT in an operant chamber, with the goal to test complex decision-making processes within a single session, as in the original human IGT. This model offers the advantage to allow a rapid assessment of the decision-making process, measuring the time-course of decisions, from random choice to a majority of choices for the preferred options, within 1 h. Because decision-making can be measured in only one session, this task is particularly suitable for quickly identifying individual differences, or for the search of the neural bases of the time-course process of decision-making, using cellular brain imaging or PET scanning. Performances in this task are stable and reproducible (Rivalan et al., 2009a, 2011). This task can be solved by the majority of rats, whereas some poor decision-makers that prefer larger immediate rewards despite suffering large losses can be identified, a result also observed in humans (Bechara et al., 1999, 2001; Bechara and Damasio, 2002; Davis et al., 2007; Glicksohn et al., 2007).

The test requires the rat to deduce, by trial and error, among four options, the two that are the more rewarding on the long-term and tracks the continuous and dynamic process of deduction and readjustment of choice. The principle of the task tightly mimics that of the human IGT: the contingencies are arranged so that the two options (holes chosen by nose-poking) that steadily offer bigger immediate food reward, are disadvantageous in the long run due to higher unpredictable penalties (frustrating time-outs during which no reward can be obtained). Inversely, the two advantageous options steadily offer smaller reward, but unpredictable penalties that can follow are shorter.

The testing apparatus (**Figure 4**) consists of an operant chamber lightly adapted from a standard five-hole operant chamber usually used for the five-choice serial reaction time task (Imetronic, Pessac, France). The adaptation consists of blocking the access to the central hole by a panel, and adding a transparent vertical partition containing a central opening that divides the chamber in half to allow an equal distance to each hole. The four holes, that can be dimly illuminated, are available on a curved wall, with a food dispenser on the opposite wall. The holes and food magazine are equipped with infrared sensors that detect nose-pokes. A program controls the chambers and collects the data.

Rewards are represented by the delivery of palatable food pellets (TestDiet, formula P), while punishments are associated with time-out periods, during which nose-pokes are inactive. As in the original IGT, each selection is rewarded, and some are also unpredictably punished. Similarly to $RGT_{\textit{reward probabilities}}$, training for the acquisition of the basic operant responses is performed before *testing*. During these daily sessions (30 min each, repeated until a learning criterion is obtained within a session) animals are trained to associate two consecutive nose-pokes (ensuring voluntary choice performance) in any of the four illuminated holes with the delivery of one food pellet. Once the learning criterion is reached, animals are habituated to variable reward amounts (one/two pellets) per selection (two 15-min block per reward amount). Although a preference for a side could be observed individually, it has repeatedly been shown that this preference had no consequences on performances during test, nor differences in the level of exploration. Moreover, because palatable food pellets are used, food restriction facilitate training but is not necessary for testing (Rivalan et al., 2009a). During the subsequent test session (1 h of duration), animals are again requested to freely *choose* among the available options, but advantageous and disadvantageous selection schedules are now introduced. On one side of the curved wall, advantageous options are associated with the immediate delivery of only one pellet, that can eventually be followed by short time-outs ("deck C": 12-s time-out 25% of the trials; "deck D": 6-s time-out 50% of the trials). These two choices result in the same theoretical maximum gain of about 300 pellets in 1 h. On the other side of the curved wall, disadvantageous options correspond to two response holes that always provide two pellets as a reward upon selection, but that can eventually be followed by

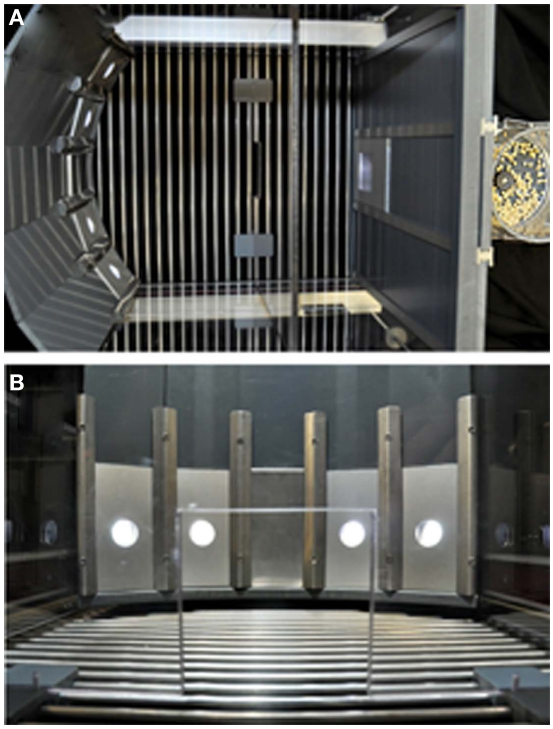

FIGURE 4 | The four-hole operant chamber model ($RGT_{\text{one session reward and time-out}}$). (A) Top view of the apparatus (Imetronic). These chambers are modular and can be configured for multiple behavioral paradigms (one or several nose-poke or levers, drug self-administration). A transparent vertical partition containing a central opening divides the chamber in half with four holes on a curved wall on a side, and a food dispenser on the opposite wall. **(B)** The four holes, that can be dimly illuminated, are equidistant from the central opening.

long time-outs ("deck A": 222-s time-out 50% of the trials; "deck B": 444-s time-out 25% of the trials). These two options have the same theoretical maximum gain of about 60 pellets in 1 h. Punishments are assigned to each selection in a pseudo-random manner, so to maintain immediate outcome unpredictability, thus, options are not "stacked" to favor reward delivery at the beginning of the session (see Fellows and Farah, 2005). A choice also results in the deactivation of all stimulus-lights except for the chosen hole, until the reward is collected. This is particularly important during the time-outs to facilitate the association between hole response and its consequences. Based on the reinforcement schedule employed during testing, choosing either advantageous or disadvantageous options during this session would result in a theoretical overall payoff ratio of 5.00 (300 or 60 pellets per response hole, considering a standard trial duration of 9 s). The task difficulty can be easily modified, i.e., decreasing the ratio to 3 by increasing time-out duration associated with favorable options, that lead to a slower decision-making process (see Rivalan et al., 2009a).

MULTIPLE SESSION CHOICE FOR CONFLICT BETWEEN OPTIONS VARYING IN REWARD AND TIME-OUT FREQUENCY AND DURATION: THE FIVE-HOLE OPERANT CHAMBER MODEL ($RGT_{REWARD\ OR\ TIME\text{-}OUT}$)

This rodent gambling task also signals loss on non-rewarded trials through the presentation of frustrating time-out periods, and uses sucrose pellets as a reward. This model presents the animals with a choice between four distinct options on each trial which are loosely analogous to the four deck of cards in the IGT, i.e., the options differ in terms of the probability and magnitude of expected gains and losses, such that the two options which deliver the smaller units of reward are ultimately advantageous. However, this model differs both in the duration of training, the reinforcement contingencies associated with the different options and the way in which the task is learned. Although both the $RGT_{one\ session\ reward\ and\ time\text{-}out}$ and $RGT_{reward\ or\ time\text{-}out}$ are complementary, they also have different strengths and can be best used to answer different questions. Notably, the $RGT_{reward\ or\ time\text{-}out}$ model was designed in a manner that could be optimized for behavioral pharmacology experiments and other manipulations, which benefit from repeated daily testing.

Testing takes place in standard five-hole operant chambers available from a number of vendors (e.g., Med Associates, Coulbourn; the same chambers used for the five-choice serial reaction time task; **Figure 5**). The defining feature of such boxes is that an array of five stimulus–response holes is located on one wall of the chamber, although only four holes are used during the task. Each response hole can be illuminated by a stimulus light located therein, and nose-poke responses into a hole are detected by an infrared sensor. A food tray, also equipped with an infrared sensor and a tray light, is located in the middle of the opposite wall, into which sucrose pellets can be delivered via an external pellet dispenser. The entire chamber can also illuminated using a house-light.

As is often standard for operant-based tasks, animals are first trained to make the basic operant response, in this case to make a nose-poke response into a single illuminated response hole within 10 s. Animals are then trained on a forced-choice version of the task for five to seven sessions, during which only one of the four possible options is presented on each trial (Zeeb et al., 2009; Zeeb and Winstanley, 2011). This training stage ensures that all animals equally experience each of the four reinforcement contingencies, in order to prevent simple biases toward a particular hole from developing. Although this forced-choice contingency does not occur in the IGT, subjects are verbally instructed that there are decks which result in greater losses than others and that winning may be accomplished if the worst decks are avoided (Bechara et al., 1999).

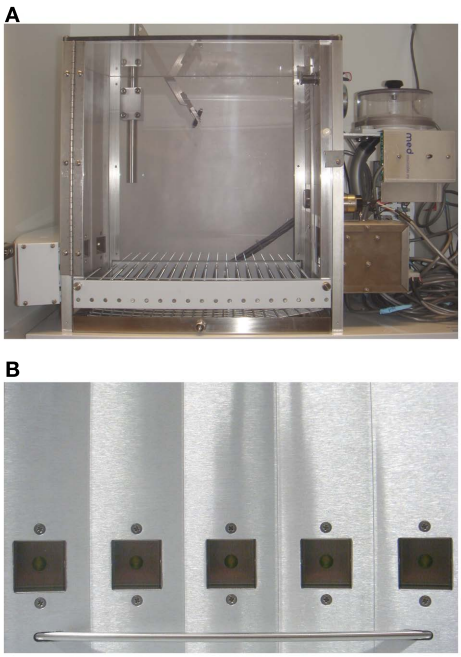

FIGURE 5 | The standard five-hole operant chamber, as used for the $RGT_{reward\ or\ time\text{-}out}$ model. (A) Side view of a Med Associates five-hole box. These chambers are modular and can be configured for multiple behavioral paradigms and manipulations, hence the arm assembly for drug self-administration/microdialysis and additional levers visible. However, these components are not necessary for the RGT. **(B)** A close-up of the standard five-hole array showing stimulus light location and infrared beam.

Following forced-choice training, all animals are then tested on the free-choice task, where all four options are presented (i.e., all four response holes are illuminated). Training occurs once daily, and each session lasts for 30 min. Animals initiate each trial by making a nose-poke response into the illuminated food tray. This response initiates a 5-s ITI, where all lights are off and the chamber is in darkness. A nose-poke response in any hole of the array during this time is termed a premature response – a measure of motor impulsivity – and is signaled by illumination of the house-light for 5 s. The animal must then re-start another trial (by making a nose-poke response in the illuminated food tray). This measurement is analogous to that of the premature responses measured in the five-choice serial reaction time task (Robbins, 2002). Therefore, for the first time, both motor impulsivity and decision-making can be concurrently assessed – and dissociated – within the same task (Zeeb et al., 2009).

At the end of the ITI, four holes are concurrently illuminated (left to right: holes 1, 2, 4, and 5) for a maximum of 10 s. The animal signals its preference by nose-poking in one of the illuminated holes, at which point all the stimulus-lights are then extinguished.

If the trial is rewarded, the tray light illuminates and the corresponding number of sucrose pellets are delivered immediately. As in the five-choice serial reaction time task, responding at the food tray to collect reward also initiates the next trial. However, if the trial is a loss, no reward is delivered and a time-out period begins during which the light in the hole chosen flashes at a frequency of 0.5 Hz. The animal is unable to initiate any more trials or earn reward until the time-out is over, at which the animal can initiate the next trial by responding in the now-illuminated food tray. The reinforcement contingency linked to each option (response hole) varies in terms of both the number of sugar pellets available, and the duration and probability of a punishing time-out period. The probability of receiving reward or punishment remains constant throughout each session, i.e., the options are not "stacked" to favor reward delivery at the beginning of the session (see Fellows and Farah, 2005). The spatial location of these options are balanced, such that one advantageous and one disadvantageous option is located on each side of the chamber, therefore the correct strategy cannot be reduced to a side bias. The optimal strategy is to select the two-pellet option (P2), associated with a 10-s time-out period that occurs 20% of the time (80% chance of winning). The next best option is P1 (5 s time-out, 90% chance of winning). The two highly disadvantageous options are both associated with larger immediate gain – three or four sucrose pellets – but also longer time-out periods (P3: 30 s time-out, 50% chance of winning; P4: 40 s time-out; 40% chance of winning). Occurrence of gains and losses on each trial is determined pseudo-randomly to ensure a constant distribution of gains and losses throughout each session.

It is possible to calculate the hypothetical amount of reward that could be obtained if an option is chosen exclusively in a 30-min training session, and if each trial is initiated and performed as quickly as possible (i.e., within 5 s; Zeeb et al., 2009). Based on these calculations, persistent selection of the optimal choice (P2) yields a hypothetical maximum of 411 sugar pellets, whereas P1 yields 295 pellets. The two disadvantageous options are associated with significantly less possible reward (P3: 135 pellets; P4: 99 pellets). Therefore, the optimal strategy is to prefer the advantageous options – P2 and P1 – which are associated with smaller, immediate gain, but also less punishment resulting in more reward in the long-term, while avoiding the tempting, yet disadvantageous, large reward options associated with greater loss – P3 and P4.

RGT VALIDITY

CRITERIA FOR THE VALIDITY OF AN ANIMAL MODEL

The goal of an animal model of human decision-making is to develop, in laboratory animals, behavior that closely resembles that observed in human subjects, thereby allowing researchers to translate findings across species. The validity of animal models depends on the strict definition of its potential applications, taking into account the models' biases and limits. This validity is commonly assessed using the concept of face, construct and predictive validities (McKinney and Bunney, 1969; Willner, 1995). Face validity refers to similarities between animals and humans in symptomatology, construct validity concerns similarities in underlying psychobiological and physiological processes, and predictive validity concerns the model's potential to predict these processes in human, most often with regards to identifying efficient pharmacological compounds in humans. With respect to face validity, numerous studies using the IGT in both healthy and patient populations provide knowledge regarding task performance and distinct behavioral patterns of impairment that allows direct comparison to response patterns in the rodent tasks. However, when it comes to construct and predictive validities, current knowledge from pharmacological or imaging human studies is incomplete, making these attributes more difficult to assess. The gap in our current understanding of the neurobiological underpinnings of decision-making in fact underlines the need for animal models that allow more thorough and controlled investigation of these mechanisms.

FACE VALIDITY OF THE RGTs

Response patterns in RGTs

In all four RGTs, despite the considerable differences in task characteristics, animals were able to evaluate which options are advantageous in the long-term, and to adapt their choice behavior accordingly. Although the end point of behavioral testing differed across tasks, from decision-making measure during a single session to a multiple session learning process, most rats finally developed a significant preference for the more advantageous options (van den Bos et al., 2006; Pais-Vieira et al., 2007, 2009; Homberg et al., 2008; Zeeb et al., 2009; de Visser et al., 2011b; Zeeb and Winstanley, 2011), as also observed in C57BL/6 mice employing the eight-arm radial maze model (van den Bos et al., 2006) and mice performing a version very similar to $RGT_{\text{reward or time-out}}$ (Young et al., 2011).

In $RGT_{\text{reward or quinine}}$ rats start off with an explorative search profile, displaying equal preference for either the advantageous or disadvantageous arm. After 60–80 trials, a stable preference for the advantageous arm emerges. Rats' performance of $RGT_{\text{one session reward and time-out}}$ indicates that, although most animals learn the contingencies and gradually develop a preference for the advantageous options (Rivalan et al., 2009a), about 40% of the animals failed to solve the task, either because they did not develop any option preference, or because they developed a significant preference for disadvantageous options. These inter-individual differences are stable across time, and reproducible across groups. Interestingly, failure to solve the IGT by a portion (20–30%) of healthy humans has also been observed (Bechara et al., 1998, 2001, 2002; Crone and van der Molen, 2004; Dunn et al., 2006). These individuals have been characterized as impulsive and sensation-seekers (Davis et al., 2007; Franken et al., 2008), some behavioral traits that are related to those of poor decision-makers in rats, i.e., risk-taking and sensitivity to reward (Dellu et al., 1993, 1996; Rivalan et al., 2009a).

In $RGT_{\text{reward or time-out}}$, although an initial preference for the advantageous options is already established in the initial training sessions, this preference continues to develop as testing proceeds. In this experimental design, learning of options' contingencies is made prior the decision-making test, by systematically exposing animals to the task contingencies during forced-choice training sessions (Zeeb et al., 2009). This ensures that all animals have equal exposure to the different reinforcement contingencies associated with all the options, and theoretically prevents the development of any biases due to inadequate sampling. As a result, it can be argued that performance in this task predominantly captures the second phase of the IGT when contingencies are known (exploitation), particularly later in training

when performance has stabilized. However, the fact that choice between the options still varies between sessions earlier in training implies that learning (exploration) still occurs. Furthermore, recent evidence suggests that acquisition and performance of this task is controlled by somewhat dissociable neural circuitry (Zeeb and Winstanley, 2011) which supports the distinction between brain areas involved in exploration vs. exploitation outlined in Section "Neural Substrates."

In the $RGT_{\text{reward probabilities}}$, the outcome difference between advantageous and disadvantageous options is minimal (8 vs. 9 pellets), an inconsistency with respect to the human IGT where choice options have marked long-term outcome differences. As such, this task may be more similar to models of probability discounting (e.g., St Onge and Floresco, 2009b) and other aspects of decision-making under uncertainty, rather than the IGT. Nevertheless, control rats preferentially choose smaller but more reliable rewards over larger unreliable rewards, similar to the choice pattern observed in humans. In summary, in all four RGTs animals are able to learn which options are advantageous in the long-term, but the nature of the learning patterns differs between the tasks. This source of variation could be used to address more specifically one aspect of a deficit in animal models of psychiatric conditions, as observed in mental disorders. For example, preference for disadvantageous options, as observed in schizophrenia, OCD, pathological gambling, substance abusing individuals, or ADHD, can be tested in RGTs with a high ratio between advantageous vs. disadvantageous options; slower IGT decision-making in maniac or substance-dependent individuals could be addressed in $RGT_{\text{one session reward and time-out}}$ with similar time-course of decision process; sensitivity to the frequency of the punishment as observed in ADHD or schizophrenic patients (Shurman et al., 2005; Toplak et al., 2005) could be assessed in $RGT_{\text{reward probabilities}}$.

Influence of sex and inter-individual differences on RGT performance

The only task which has been used to study sex differences to date is the $RGT_{\text{reward or quinine}}$. The overall pattern of data matches some findings in humans in that females display poorer performance as compared to males (Reavis and Overman, 2001; Bolla et al., 2004; van den Bos et al., 2007; de Visser et al., 2010). Both in rats and humans, sex differences emerge in the second part of the task and have therefore been related to diminished cognitive control in females vs. males (van den Bos et al., 2007; de Visser et al., 2010).

Based on findings from human IGT studies, it is well established that inter-individual differences in personality traits, such as trait anxiety, risk-taking, and impulsivity affect performance. The relationship between certain individual trait differences and decision-making performance has been investigated in both the $RGT_{\text{one session reward and time-out}}$ and $RGT_{\text{reward or quinine}}$ models. Associations between risk-taking, reward sensitivity, and IGT performance were demonstrated in male Wistar rats in the $RGT_{\text{one session reward and time-out}}$ (Rivalan et al., 2009a). When compared to good decision-makers, animals performing poorly in this task were also more sensitive to rewards, as they ran faster to obtain a food reward in a runway paradigm and sustained higher amounts of effort to earn food in the context of a progressive ratio schedule of food reinforcement. Moreover, these individuals were more risk-prone, exposing themselves more frequently to potentially dangerous environments in the light/dark emergence test (highly illuminated compartment; Dellu et al., 1993) and in the elevated plus-maze test (external third of the open arms; Rivalan et al., 2009a). These data are consistent with findings from healthy human studies, showing that poor IGT performers also exhibit riskier choice patterns in two tasks assessing decision-making under risk, the Game of Dice Task (Brand et al., 2007b) and the Cups task (Weller et al., 2010), and the observation that in both healthy and clinical populations exhibiting poor decision-making, reward hypersensitivity appears to underlie deficits in IGT performance (Must et al., 2006; Davis et al., 2007; Suhr and Tsanadis, 2007; Kobayakawa et al., 2010). Furthermore, abnormal levels of risk-taking and hypersensitivity to reward are found in psychiatric disorders associated with poor decision-making and impulsivity, such as ADHD, substance abuse, pathological gambling, or mania (Mazas et al., 2000; Bechara et al., 2001; Drechsler et al., 2008; Kathleen Holmes et al., 2009). Hence, it could be argued that poor decision-making in both humans and rats may stem from common risk factors to develop these disorders.

In a recent study, high levels of anxiety as measured with standard parameters in the elevated plus-maze (% time and visits in open arms) has been associated with poor decision-making using the $RGT_{\text{reward or quinine}}$ model (de Visser et al., 2011b). Based on a detailed analysis of rat choice strategies, it was suggested that highly anxious subjects may have a shifted bias toward responding to the negatively valued stimuli, i.e., the quinine pellets, and under-appraised the positively valued stimuli, i.e., the sucrose rewards, leading to suboptimal decision-making. These findings are in line with human data, in that highly anxious healthy subjects performed worse on the IGT compared to their less anxious counterparts (de Visser et al., 2010). These reports also highlight the potential confound in the human data, in that both high anxiety (preferentially measured in the experimental paradigm of de Visser et al., 2011b), and high risk seeking (preferentially measured by Rivalan et al., 2009a) are associated with poor IGT performance, an issue that *animal* models may be able to resolve, and future work will no doubt address the biological basis of these findings.

Taken together, RGT performance, similar to the IGT, is associated with inter-individual differences related to sex differences and behavioral traits. The study of these inter-individual differences provide a reliable and valuable tool to investigate, for instance, the neurobiological features of subjects at risk to develop mental disorders related to poor decision-making.

CONSTRUCT VALIDITY OF THE RGTs

Construct validity of the RGTs can be evaluated based on the partial knowledge of the neurobiological mechanisms underlying IGT performance in humans. Key brain areas have been identified from lesion and imaging studies that include parts of the prefrontal cortex, the ventral striatum, and limbic structures such as the amygdala (see Neural Substrates). Furthermore, gene polymorphisms related to serotonergic and dopaminergic systems have been identified that modulate IGT performance and affect the function of corticolimbic neural circuits. Thus, construct validity of the RGTs will be discussed based on these findings (see **Table 2** for overview).

Table 2 | Effect of manipulations on rodent IGT performance.

Manipulation	$RGT_{reward\ or\ quinine}$	$RGT_{reward\ probabilities}$	$RGT_{one\ session\ reward\ and\ time\text{-}out}$	$RGT_{reward\ or\ time\text{-}out}$
C-FOS				
Orbitofrontal cortex	No dissociation between good and bad performers (de Visser et al., 2011b)		Dissociation good and bad performers Fitoussi et al. (in preparation)	
Medial prefrontal cortex	Dissociation good and bad performers (de Visser et al., 2011b)		Dissociation good and bad performers Fitoussi et al. (in preparation)	
Ventral striatum	Dissociation good and bad performers (de Visser et al., 2011b)		Dissociation good and bad performers Fitoussi et al. (in preparation)	
LESIONS/INACTIVATIONS				
Orbitofrontal cortex		Increased choice of higher risk option during exploitation phase (Pais-Vieira et al., 2007)	Perseverative responding (Rivalan et al., 2011)	Lesion before acquisition: delayed development of preference for the correct option. Lesion afer acquisition: no effect (Zeeb and Winstanley, 2011)
Prelimbic cortex			Inability to chose between good and bad options, or inflexibility (Rivalan et al., 2011)	
Anterior cingulate cortex			Delayed good decision-making (Rivalan et al., 2011)	
Medial prefrontal cortex	Impaired task-progression during exploitation phase (de Visser et al., 2011b)			
Amygdala				Lesion before acquisition: delayed development of preference for the correct option. Lesion after acquisition: Increase in preference for the disadvantageous options (Zeeb and Winstanley, 2011)
GENETIC ALTERATIONS				
SERT knockout rat	Increased choice of advantageous option during exploitation phase (Homberg et al., 2008)			
DAT knockout mouse				Increased choice of the disadvantageous/risky options
PHARMACOLOGY				
8-OH-DPAT (5-HT_{1A} agonist)				Less advantageous choices (Zeeb et al., 2009)
SKF 81297 and quinpirole or bromocriptine (D_1, $D_{2/3}$ agonists)				No effect (Zeeb et al., 2009)
Eticlopride (D_2 antagonist)				Improved choice advantageous option (Zeeb et al., 2009)
Amphetamine				Increased choice of less advantageous options (Zeeb et al., 2009)
NBI27914 (CRF1 antagonist)		Intra amygdala administration (BLA) reversed poor performance (Ji et al., 2010)		

Serotonergic system and RGT

It is possible to draw a parallel between performances of rats lacking the SERT in the $RGT_{reward\ or\ quinine}$ (Homberg et al., 2008) and the 5-HTTLPR (serotonin-transporter-linked polymorphic region) IGT studies in humans. Homozygous ($SERT^{-/-}$) and heterozygous ($SERT^{+/-}$) knockout rats are suggested to model stressed and unstressed 5-HTTLPR s-allele carriers, while wild-type control rats may correspond to 5-HTTLPR l-allele carriers (Kalueff et al., 2009; Homberg and Lesch, 2010). $SERT^{-/-}$ and $SERT^{+/-}$ rodents show gene-dose-dependent increases in extracellular serotonin levels due to reduced serotonin reuptake (Homberg et al., 2007). It was found that $SERT^{+/-}$ and $SERT^{-/-}$ rats demonstrated better decision-making compared to $SERT^{+/+}$ animals, particularly in the second half of the trials. This seemingly contrasts findings that human 5-HTTLPR s-allele carriers performed worse during the task compared to l/l subjects (Must et al., 2007; da Rocha et al., 2008; Homberg et al., 2008; van den Bos et al., 2009b; He et al., 2010). If serotonin modulates vigilance and is responsible for the integration of relevant environmental stimuli (Branchi, 2010; Homberg and Lesch, 2010), this discrepancy may be reconciled by the fact that $RGT_{reward\ or\ quinine}$ employs two baited choice options, as opposed to four in the human IGT. In the $RGT_{reward\ or\ quinine}$, the $SERT^{-/-}$, and $SERT^{+/-}$ rats may not have been distracted by environmental stimuli, such that they could focus on their long-term goal: obtaining maximum gain. It would be interesting to test this hypothesis in one of the RGT models which require animals to discriminate between four options concurrently, such as the $RGT_{one\ session\ reward\ and\ time\text{-}out}$ or $RGT_{reward\ or\ time\text{-}out}$.

Dopaminergic system and RGT

As discussed earlier, increased choice of the disadvantageous options on the IGT has been reported in bipolar patients. Reduced dopamine transporter (DAT) function has been hypothesized as a contributing factor to bipolar disorder on the basis of both genetic linkage studies (Kelsoe et al., 1996; Greenwood et al., 2001, 2006) and analysis of DAT expression in patients (Horschitz et al., 2005). Using a mouse version of the $RGT_{reward\ or\ time\text{-}out}$, increased choice of the disadvantageous, or risky, options has been observed in mice lacking the DAT (Young et al., 2011). Furthermore, this risky decision-making correlated with specific exploratory activity in a mouse behavioral pattern monitor (BPM), a pattern of motor behavior that is also observed in acutely manic patients (Perry et al., 2009). Hence, this RGT model has proven useful in demonstrating similar behavioral phenotypes in a putative mouse model of bipolar disorder as compared to the clinical condition.

Prefrontal cortex and RGT

Evidence of involvement of the prefrontal cortex in rodent IGT-like decision-making was reported in three RGT studies. OFC lesioned animals preferred the higher risk lever during the second phase of the task in the $RGT_{reward\ probabilities}$ (Pais-Vieira et al., 2007). This is in accordance with impaired decision-making and high risk-taking observed in human patients with damage to the vmPFC (Bechara et al., 2000; Clark et al., 2008), and the relationships between OFC activity and IGT performance in healthy subjects in fMRI studies (Bolla et al., 2004; Lawrence et al., 2009). Theoretically, OFC lesion effect on risk-taking could be expressed in the $RGT_{reward\ probabilities}$, since this task is based on a two-option simple choice as opposed to the $RGT_{one\ session\ reward\ and\ time\text{-}out}$ (Rivalan et al., 2011). In this latter task, measure of risk-taking is combined with the capacity to perceive the changes in contingencies between training (all options have the same consequences) and test (four different consequences), a function also associated with OFC (see below). Consequently, OFC lesioned rats exhibited perseverative responding, as if they failed to encode the change in contingency. This was demonstrated by an absence of sampling of the four options at the beginning of the test, and a marked preference for the holes on the side that they preferred during training. Such inflexible responding following OFC lesions has been reported multiple times, particularly in the context of impaired reversal learning (Dias et al., 1996; Schoenbaum et al., 2002; McAlonan and Brown, 2003; Ragozzino, 2007; Rudebeck and Murray, 2008; Kazama and Bachevalier, 2009; Robbins and Arnsten, 2009). Indeed, the original demonstration that vmPFC-damaged patients were impaired on the IGT used stacked decks, such that no losses were experienced in the first block of trials, and all subjects initially preferred the large reward decks (Bechara et al., 1999). Patients with comparable vmPFC damage were not impaired on a "shuffled" version of the IGT, in which gains and losses were distributed randomly through the decks, suggesting that the original impairment arose from patient's inability to switch preferences away from the disadvantageous decks once punishments were introduced (Fellows and Farah, 2005). Considerable evidence suggests that this region is critical in generating outcome expectancies, and updating them as the reward value of *available options* changes (for review see Schoenbaum et al., 2009). Notably, the degree of OFC involvement may depend on the level of ambiguity experienced by the subject, i.e., the OFC may be important when individuals are learning the reinforcement contingencies and ambiguity is high. Once uncertainty becomes expected, such that the individual figures out the odds of risk and reward associated with each option, the OFC may play less of a role in maintaining the optimal choice strategy. This hypothesis is supported by recent findings using $RGT_{reward\ or\ time\text{-}out}$ in which OFC lesions performed prior to acquisition of the task slowed learning such that rats took longer to develop a strong preference for the correct option (Zeeb and Winstanley, 2011). However, if lesions were performed once the task had already been learned, then no choice impairment was observed. Furthermore, in $RGT_{reward\ or\ quinine}$, final task performance was not related to OFC activation, as measured by the levels of expression of the immediate early gene c-fos (de Visser et al., 2011b), again indicating that activity within the OFC is not a critical determinant of decision-making under risk. Conversely, under risk and ambiguity in the $RGT_{one\ session\ reward\ and\ time\text{-}out}$, c-fos expression differentiated between good and poor decision-makers (Fitoussi et al., in preparation).

In addition to the OFC, damage to two areas of the medial PFC (mPFC) were found to affect performance of the $RGT_{one\ session\ reward\ and\ time\text{-}out}$: the prelimbic cortex [a primitive version of the dlPFC of the primate (Vertes, 2006)] and the ACC (Rivalan et al., 2011). Lesions of the ACC mainly delayed good decision-making in this task whereas lesions of the prelimbic cortex either led to an inability to chose between good and bad

options (undecided behavior) or induced inflexibility in behavior, similarly to OFC lesions. Moreover, c-fos activity in the mPFC was found to differentiate between good and poor performers in the $RGT_{reward\ or\ quinine}$ and $RGT_{one\ session\ reward\ and\ time\text{-}out}$ (de Visser et al., 2011b; Fitoussi et al., in preparation). Interestingly, the rat mPFC shares anatomical and functional homology with the ACC and dlPFC in humans (Uylings and van Eden, 1990; Brown and Bowman, 2002; Uylings et al., 2003). These areas are involved in IGT performance in humans (Ernst et al., 2002; Bolla et al., 2004; Fukui et al., 2005; Lin et al., 2008; Lawrence et al., 2009). The ACC and dlPFC are specifically involved in a negative feedback circuit of cortical control over limbic areas (Ridderinkhof et al., 2004; Bechara et al., 2005). This top-down cognitive control circuit controls decision-making on the basis of reward and punishment (Quirk et al., 2000; Miller and Cohen, 2001; Rogers et al., 2004; St Onge and Floresco, 2009a; Davis et al., 2010) and is suggested to mediate predominantly the second part of the IGT, when a preference for the advantageous decks has developed and performance is mainly characterized by maintenance and exploitation of the advantageous choice strategy (van den Bos et al., 2007). Thus, activation differences in the mPFC in rats in the RGT may be related to a weaker cognitive control system in poor vs. good performers. In line with the aforegoing, inactivation of the mPFC using a mixture of GABA-agonists muscimol and baclofen, hampered task-progression in those animals which already showed task-learning but not in those animals which were still in the exploratory phase of the task (de Visser et al., 2011a). Further experiments are needed to substantiate the role of the mPFC in decision-making using the different RGT models.

Sub-cortical areas and RGT

Apart from cortical areas, the ventral striatum was found to be differentially recruited in good vs. poor performers in $RGT_{reward\ or\ quinine}$ (de Visser et al., 2011b). More specifically, c-fos induced activation was higher in the nucleus accumbens core (NaC) but lower in the nucleus accumbens shell (NaS) in good performers compared to poor performers, suggesting distinct roles for the nucleus accumbens subareas in rat decision-making. As Yin et al. (2008) argued, the NaC may be involved in more advanced decision-making processes than the shell, thus reflecting the more advanced performance of the good decision-makers. Moreover, the NaC has been implicated in impulse control and behavioral flexibility (Cardinal et al., 2001; Christakou et al., 2004; Pothuizen et al., 2005; Floresco et al., 2006), but see (Murphy et al., 2008), which may suggest that good decision-makers are better at developing a behavioral strategy that is directed to the long-term gain of the advantageous option as opposed to the immediate gain of the disadvantageous option.

The amygdala has also been associated with IGT performance, in that patients with bilateral lesions to this brain region showed a very similar pattern of choice on the IGT as vmPFC patients, choosing more often from the disadvantageous decks (Bechara et al., 1999). A similar pattern of choice has recently been observed using the $RGT_{reward\ or\ time\text{-}out}$ following bilateral lesions to the BLA, in that lesions made after animals had acquired the task lead to an increase in preference for the disadvantageous options. Interestingly, lesions made prior to acquisition of the task strongly resembled the effects of OFC lesions made at the same time point, in that both groups of lesioned animals were slower to adopt the correct strategy as compared to sham controls (Zeeb and Winstanley, 2011). Such data suggest that the OFC and BLA may be working together to optimize choice behavior when the odds of reinforcement are still unclear. These results are in accordance with the finding that the level of ambiguity in choices was positively correlated with the level of activity in the OFC and amygdala (Hsu et al., 2005; Lawrence et al., 2009). The fact that BLA lesions still affected decision-making once the task had been learned suggests that decreased activity in this region may precipitate an increase in risky choice, and that this area is involved in maintaining an optimal decision-making strategy under risk even after the cost–benefit contingencies have been acquired.

In conclusion, neural circuitry comprising the PFC, striatum, and amygdala appears to modulate decision-making in RGT models, and the effects observed are largely consistent with findings in humans. Altered connectivity between cortico-striatal-limbic circuitry has been implicated in various disorders, such as schizophrenia, drug addiction, OCD, and anxiety disorders. The RGTs may therefore contribute to an increased understanding of the pathophysiology of these disorders. Comparing the findings of lesion and c-fos activation studies across the RGT models will help to further validate their use, and may provide new insight into the neural circuitry involved in this form of decision-making. Moreover, the somatic marker hypothesis could be addressed in all the RGTs during the exploration phase of the tasks, i.e., when choices evolve with time before reaching a stable level (exploitation phase). Measures of blood pressure, heart rate, associated with behavioral activity could serve as somatic markers in freely moving rats, by radiotelemetry.

PREDICTIVE VALIDITY OF THE RGTs

Given that low serotonin (5-HT) function has been observed in problem gamblers, and that selective 5-HT reuptake inhibitors are currently used as a treatment for this disorder, Zeeb et al. (2009) investigated the effects of acutely decreasing 5-HT release using the 5-HT_{1A} receptor agonist 8-OH-DPAT on performance of the $RGT_{reward\ or\ time\text{-}out}$. This compound impaired performance, significantly increasing choice of less advantageous options (P1, P3) and decreasing choice of the best option (P2). These effects were effectively blocked by co-treatment with the highly selective 5-HT_{1A} receptor antagonist WAY100635. However, it remains to be established whether these effects are due to activation of inhibitory 5-HT_{1A} receptors located pre-synaptically in the raphe nuclei, or post-synaptically in limbic and cortical brain regions.

In addition to the effects of acute 5-HT manipulations, the effects of receptor-specific dopamine agonists and antagonists have also been explored using $RGT_{reward\ or\ time\text{-}out}$ (Zeeb et al., 2009). Interestingly, D_1 and D_2/D_3 receptor agonists (SKF 81297 and quinpirole or bromocriptine) did not affect animals' choice preferences on the task. However, acute administration of the D_2 receptor antagonist, eticlopride, significantly improved task performance by increasing the animals preference for the optimal option (P2) while decreasing choice of both high reward–high punishment options (P3, P4). This effect appears to be selective to the blockade of D_2 receptors, as administration of a D_1 receptor

antagonist, SCH 23390, did not alter decision-making (Zeeb et al., 2009).

The psychostimulant amphetamine has been shown to prime the motivation to play slot machines in pathological gamblers (Zack and Poulos, 2009). Amphetamine treatment significantly impaired the animals' ability to perform the $RGT_{reward\ or\ time\text{-}out}$ optimally. However, in contrast to the effects of the 5-HT_{1A} receptor agonist 8-OH-DPAT, amphetamine caused animals to become more punishment/loss-sensitive, illustrated by an increased preference for P1, the option with the smallest amount of immediate reward, but also the least amount (frequency and duration) of punishment. Therefore, amphetamine may amplify animals' sensitivity to punishment (Zeeb et al., 2009). Although this behavior cannot necessarily be classified as "risky," placing too much emphasis on a potential loss may be unfavorable in the long-term (Kuhnen and Knutson, 2005) and can contribute to loss-chasing behavior in real-life gambling situations (see discussion in Campbell-Meiklejohn et al., 2008).

Overall, there are both similarities and discrepancies when comparing these results to human findings. As previously discussed, high levels of prefrontal dopamine and corticolimbic 5-HT levels may correlate with worse IGT performance. Therefore, the fact that amphetamine impaired decision-making on $RGT_{reward\ or\ time\text{-}out}$ supports the hypothesis that increased levels of dopamine or 5-HT impairs decision-making. However, acutely decreasing dopamine levels in healthy volunteers by BCAA administration causes subjects to choose the disadvantageous options on the IGT, especially during the exploitation phase of testing (Sevy et al., 2006). One explanation provided by Zeeb et al. (2009), is that the effects of various drug manipulations may rely on both the basal levels of dopamine as well as task-related changes in dopamine release. Therefore, the effects of dopamine, and perhaps 5-HT, may follow an inverted U-shaped curve (see Neuromodulators). Interestingly, it is unclear whether an acute dose of eticlopride is modulating activity of inhibitory D_2 autoreceptors and/or post-synaptic receptors. A blockade of D_2 autoreceptors may stimulate the firing of dopaminergic neurons, while suppressing dopamine transmission post-synaptically (Seamans and Yang, 2004). The net effect may be an enhancement of prediction error signals, which would thus improve decision-making. It should be noted that high PFC dopamine levels are proposed to enhance exploration in the direction of alternative options that might yield higher gains (Frank et al., 2009); however pharmacological manipulations were performed once animals had been trained on the $RGT_{reward\ or\ time\text{-}out}$, and therefore did not assess the ability of these drugs to alter task acquisition.

As amphetamine increased the saliency of the punishment signals in $RGT_{reward\ or\ time\text{-}out}$, it may be suggested that this effect was caused by an abnormal increase in dopamine. However, this explanation contrasts with the finding that COMT Met/Met individuals have an attentional imbalance in favor of rewards (van den Bos et al., 2009b). One possible explanation is that amphetamine may be causing rats to become more risk-averse through increases in other neurotransmitters (such as 5-HT). Another possibility is that animals received an acute treatment in the study by Zeeb et al. (2009), whereas the human subjects tested in the study by van den Bos et al. (2009a) was observing the effects of long-term genetic abnormalities. Furthermore, the COMT polymorphism is known to target the prefrontal cortex, whereas an acute dose of amphetamine would have more widespread effects.

5-HT mediates a variety of central processes, such as emotion-regulation, learning and memory, motivation, and behavioral inhibition; these traits may be unified by sensitivity to external and internal environmental stimuli, and integrated in order to facilitate associative learning processes (Branchi, 2010; Homberg and Lesch, 2010). While serotonin may modulate behavioral flexibility (e.g., Borg et al., 2009; Jedema et al., 2009) by such a mechanism, it may have less of a role when a subject has to deal with a myriad of stimuli. However, the 5-HT system is known to be involved in the emotional response to aversive events (Cools et al., 2008). As both the IGT and RGTs require subjects to integrate multiple stimuli (e.g., reward magnitude, probability of reward, punishment duration), 5-HT may play a large role in incorporation the concept of loss, and further research should be conducted to determine the role of acute and chronic manipulations of 5-HT.

LIMITATIONS AND PITFALLS OF THE RGTs

All *of* the RGT models capture one or more features of the human IGT, and have been validated to varying degrees. However, each of the RGTs also has limitations, and no single *task* fully captures all factors present in the IGT. If these limitations are taken into account when interpreting the data, the rodent models show great promise in being able to address research questions that cannot be easily studied in humans.

One general limitation of all RGTs is that rewards are represented by food pellets – a primary reinforcer – rather than a secondary reinforcer akin to money in the IGT. Given that rodents foraging for food in uncertain environments and human behavior in decision-making tasks share several features, it could be argued that the use of food as a reward may add to the ethological validity of the tasks. Moreover, utilizing food pellets presents some practical advantages in comparison to other types of rewards, such as the possibility of precise magnitude quantification, easiness in administration, and low impact on general psychological/physical functions (in contrast with psychoactive drugs, such as amphetamine, which mimic the effects of primary reinforcers at central level but also produce major side effects, e.g., the emergence of hyperactivity). However, the incentive value of food reward normally depends on an animal's motivational state (hunger/satiety; Cardinal et al., 2002). Therefore, interpretation of choice behavior in RGT models may be confounded by this highly uncontrollable factor. Although manipulation of the animals' drive for food through the employment of different food deprivation levels has been found to have no impact on decision-making in the $RGT_{one\ session\ reward\ and\ time\text{-}out}$ model (Rivalan et al., 2009a), this has yet to be determined for the other RGT versions. On the other hand, the incentive value of money, as used in human IGTs (see below) is also subjective to individual differences in money-triggered incentive salience, therefore this may be less of a concern.

By far the biggest concern with using food pellets as rewards relates to the accuracy of any of the RGTs to model the concept of loss. In the IGT, subjects materially experience financial "wins" and "losses" every time a selection is made. The probability associated

with each trial of incurring financial penalties appears to be central for IGT performance (Fernie and Tunney, 2006): for instance, a high frequency of losses can lead human subjects to discard decks that are advantageous in the long-term (Chiu et al., 2008; Lin et al., 2009). Given that sugar pellets are instantly consumed, rather than accumulated over time and then eaten, it is impossible to take sugar pellets away from animals once they have been won, i.e., truly reproducing the sensation of loss. As iterated above, in order to model the concept of loss in the RGTs, punishment is accomplished by delivery of quinine-treated instead of normal food items ($RGT_{\text{reward or quinine}}$), the absence of reward ($RGT_{\text{reward probabilities}}$), or delays ($RGT_{\text{one session reward and time-out}}$ and $RGT_{\text{reward or time-out}}$). In all cases except for $RGT_{\text{reward probabilities}}$, an actual decrease of a positive reinforcer is achieved, since choosing disadvantageous options has a negative impact on the total amount of food pellets consumed during the test. Nevertheless, employing unpalatable food or delays cannot reproduce an absolute resource deficit as a final outcome.

Gain/loss frequencies associated with each response option can be an important determinant of choice behavior during the IGT (Chiu et al., 2008; Lin et al., 2009). Regarding this task variable in the RGT models here examined, a number of discrepancies with the original human task can be identified. For both the $RGT_{\text{reward or quinine}}$ and $RGT_{\text{reward or time-out}}$ models, the disadvantageous options are associated with large but less frequent immediate rewards but larger more frequent punishments, while the advantageous options are associated with more frequent, although smaller, gains and infrequent but smaller losses. In contrast, within the IGT, the frequency of punishment delivery is varied within advantageous and disadvantageous options, but does not vary between them, such that there is both an advantageous and disadvantageous options associated with a high and low frequency of punishment; the only variable that differs is the size of the respective rewards and punishments. From this perspective, the RGT model which best captures the reinforcement contingencies present in the IGT is the $RGT_{\text{one session reward and time-out}}$ which uses two reward sizes (1 vs. 2 pellets) and two probabilities of a penalty (0.5 and 0.25). This task would therefore be most appropriate for the investigation of the "prominent deck B" phenomenon, in which individuals find it difficult to avoid responding at the high reward deck associated with the lowest probability of punishment. However, it could be argued the probability of receiving a penalty in this RGT version is still higher than that in the IGT (0.4 and 0.1 for decks A and B respectively).

The fact that the reinforcement contingencies in the RGT models are not exactly the same as the IGT may offer some unexpected benefits. For example, in the $RGT_{\text{reward or time-out}}$ model, one of the more advantageous options (P1) involves a higher frequency of wins and shorter punishing time-out periods than the most optimal strategy (P2). Choice of P1 yields more reward than the "high risk-high reward" options (P3/P4) and certainly does not represent a "risky" choice, but is nonetheless suboptimal and may reflect risk-averse/overtly loss-sensitive decision-making. There is no such component in the IGT, but it may be of interest nonetheless. Likewise, the fact that rats in the $RGT_{\text{reward probabilities}}$ model prefer the safe option even though there is only a marginal difference in net gain between the risky and advantageous options, may likewise be informative when considering decision-making biases under uncertainty.

It can be argued for both human and rodent IGT that subjects may perform worse as a result of working memory deficits and therefore have problems incorporating previous outcomes in their subsequent choices. Indeed, humans with impaired working memory were found to perform worse on the IGT (Bechara et al., 1998; Suhr and Hammers, 2010). Furthermore, discrimination learning, reversal learning and attentional capacities, punishment and reward sensitivity may all affect performance but are difficult to dissect within the IGT. In rodents, specific tasks have been widely employed to address these processes and may be combined with RGT to elucidate how different learning and decision-processes are interweaved in a complex decision-making task like the IGT.

CONCLUSION

Poor decision-making is a core deficit of major psychiatric disorders, and the identification of the underlying neural mechanisms will importantly advance both the diagnosis and treatment of these disorders. Animal models of affective decision-making provide an important tool in achieving this goal. In this review we discussed four RGTs that model specific aspects of the human IGT. In all these tests animals appear to use strategies that resemble those used by humans. That is, initially the animals explore the different choice options, but thereafter show a consistent behavioral pattern in which they attain to a given strategy. Lesion and immunohistochemistry studies have thus far shown that RGT performance is modulated by a similar neural circuitry as in humans, involving parts of the PFC, the nucleus accumbens, and BLA. Factors like the perceived value of the wins and losses, probability and time, and the integration of this information by neuromodulators dopamine and serotonin play an important role in guiding choice.

Because carefully controlled longitudinal studies in humans are hampered by practical issues, the RGTs provide new opportunities to investigate to what extent pre-existing changes in decision-making predict the development and treatment outcome of psychopathologies under influence of genes, stress, or the availability of drugs of abuse (Potenza, 2009). Although prevention is hard to achieve, even when risk factors have been identified, improvements in diagnosis may aid in the design of individualized therapies. Obviously, much remains to be done before we are able to use RGTs for this purpose, but the growing interest, and concomitantly, the development and validation of RGTs, provide heuristically useful data. While the available RGTs need further validation, one option that should be considered is whether the different RGTs should be used in parallel, or integrated into a more uniform model to investigate the factors and mechanisms associated with impaired decision-making. One potential advantage to maintaining the different models is that they all have distinct strengths. Together, comparisons between results obtain in the different RGTs are expected to provide significant contributions to our understanding of a broad range of neuropsychiatric illnesses, which will be of great benefit to society.

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Transient inactivation of the medial prefrontal cortex affects both anxiety and decision-making in male Wistar rats

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In both humans and rats high levels of anxiety impair decision-making in the Iowa gambling task (IGT) in male subjects. Expression of the immediate early gene c-fos as marker of neural activity in rat studies indicated a role of the medial prefrontal cortex (prelimbic and infralimbic region; mPFC) in mediating the relationship between anxiety and decision-making. To delineate this relationship further and assess the underlying neurobiology in more detail, we inactivated in the present study the mPFC in male rats using a mixture of the GABA-receptor agonists muscimol and baclofen. Rats were exposed to the elevated plus maze (EPM) to measure effects on anxiety and to the rodent version of the IGT (r-IGT). Inactivation led to increased levels of anxiety on the EPM, while not affecting general activity. The effect in the r-IGT (trials 61–120) was dependent on levels of performance prior to inactivation (trial 41–60): inactivation of the mPFC hampered task performance in rats, which already showed a preference for the advantageous option, but not in rats which were still choosing in a random manner. These data suggest that the mPFC becomes more strongly involved as rats have learned task-contingencies, i.e., choose for the best long-term option. Furthermore they suggest, along with the data of our earlier study, that both anxiety and decision-making in rats are mediated through a neural circuitry including at least the mPFC. The data are discussed in relation to recent data of rodent studies on the neural circuitry underlying decision-making.

Keywords: anxiety, decision-making, rats, medial prefrontal cortex

INTRODUCTION

Recently, we (De Visser et al., 2010) and others (Miu et al., 2008; conform Haegler et al., 2010) have shown that anxiety affects decision-making. More specifically, both low and high anxious male subjects as well as high anxious female subjects perform poorly in the Iowa gambling task (IGT; De Visser et al., 2010). The IGT measures decision-making processes by simulating real-life decisions involving reward, punishment, and uncertainty of outcomes. While healthy participants learn to prefer long-term advantageous options associated with immediate moderate rewards over long-term disadvantageous options associated with immediate high rewards (Bechara et al., 1994, 1999), high anxious subjects seem to remain exploratory, while low anxious subjects appear to be risk-taking (De Visser et al., 2010; see also Rivalan et al., 2009). However, the neural underpinnings of the relationship between anxiety and decision-making remain elusive.

A number of brain areas have been implicated in both anxiety and IGT-like decision-making in humans, such as the medial prefrontal cortex (mPFC), dorso-lateral prefrontal cortex, anterior cingulate cortex, and amygdala (e.g., Bechara et al., 1999; Grachev and Apkarian, 2000; Ernst et al., 2002; Bishop et al., 2004; Bolla et al., 2004; Etkin et al., 2004; Brand et al., 2006; Lawrence et al., 2009; Li et al., 2010; Salomons et al., 2010). The anterior cingulate cortex and dorso-lateral prefrontal cortex are specifically involved in a negative feedback circuit of cortical control over limbic areas (Ridderinkhof et al., 2004; Bechara, 2005). The function of this top-down control circuit, that likely controls decision-making on the basis of reward and punishment as assessed in the IGT (Quirk et al., 2000; Miller and Cohen, 2001; Rogers et al., 2004; Davis et al., 2010; St Onge and Floresco, 2010), may be impaired in high anxious individuals (Bishop et al., 2004; Roiser et al., 2009), leading to suboptimal decision-making. In rats, the mPFC has been shown to be involved in unconditioned anxiety (Duncan et al., 1996; Jinks and McGregor, 1998; Salomons et al., 2010) and probability-based decision-making in rats (St Onge and Floresco, 2010). The mPFC in rats has been suggested to share an anatomical and functional homology to the anterior cingulate cortex and dorso-lateral prefrontal cortex in humans (Uylings and van Eden, 1990; Brown and Bowman, 2002; Uylings et al., 2003).

To address the underlying neurobiology of anxiety and decision-making we (De Visser et al., 2011) recently conducted a study in male rats combining the elevated plus maze (EPM) to assess levels of anxiety, a rodent analog of the IGT (Van den Bos et al., 2006b; Homberg et al., 2008; De Visser et al., 2011) to determine decision-making performance, and expression of the immediate early gene c-fos as marker of neural activity in

areas implicated in anxiety and decision-making. Overall, these data suggested that in high anxious-poor performing male rats among others the mPFC (prelimbic, PrL and infralimbic, IL areas) is poorly recruited during task-progression leading to suboptimal decision-making. To assess this more specifically, we transiently inactivated in this study the mPFC using a mixture of the GABA-receptor agonists muscimol ($GABA_A$ receptor) and baclofen ($GABA_B$ receptor) before rats were tested on the EPM and the r-IGT. This mixture has been shown to be effective in transiently inactivating the mPFC (e.g., St Onge and Floresco, 2010). As the mPFC is suggested to become active when rats have changed their behavioral strategy toward choosing the long-term advantageous option in the IGT (Van den Bos et al., 2006a, 2007; De Visser et al., 2010, 2011), we inactivated the mPFC in rats that either still showed exploratory behavior or rats that already showed a preference for the long-term advantageous option in the r-IGT. We predicted that inactivation of the mPFC would increase anxiety on the EPM and lead to suboptimal decision-making in the r-IGT in those rats that already showed a preference for the long-term advantageous option.

MATERIALS AND METHODS

SUBJECTS

Male Wistar rats ($n = 30$), 10 weeks of age, were purchased from Harlan (Horst, the Netherlands). They were housed individually in Makrolon type IV cages under a reversed 12 h light/dark cycle (lights off at 7 am). A shelter and paper tissues were provided as cage enrichment. Food and water were freely available except during testing (see below). Room temperature was controlled at 21 ± 2°C with a relative humidity of 60 ± 15%. A radio provided background noise. All experiments were approved by the Animal Ethics Committee of Utrecht University and were conducted in agreement with Dutch laws (Wet op de Dierproeven, 1996) and European regulations (Guideline 86/609/EEC).

EXPERIMENTAL PROCEDURE

After arrival, rats were allowed to habituate to the housing conditions in the animal facility for 2–3 weeks. Cages were cleaned once a week. Rats were handled two to three times a week to familiarize them with the experimenters. After this habituation period, surgery followed. All rats were allowed to recover for at least 10 days before behavioral testing started. During this recovery period, animals were handled daily and habituated to the infusion procedure. Rats were then tested on the EPM. One week later, rats were tested in the rodent IGT (r-IGT) for 2 weeks under mild food restriction. All experiments were carried out during the dark phase of the day–night cycle, between 8.30 am and 5 pm.

Surgery

Rats (380–420 g) were anesthetized using a mixture of fentanyl (0.25 mg/kg, i.p., Fentanyl Bipharma, Hameln Pharmaceuticals GmbH, Hameln, Germany, 0.05 mg/mL fentanyl citrate) and dexmedetomidine (0.15 mg/kg, i.p., Dexdomitor®, Pfizer Animal Health BV, Capelle a/d IJssel, the Netherlands, 1 mg/mL medetomidine hydrochloride). Further induction of anesthesia was carried out when necessary by administration via mask inhalation of isoflurane (IsoFlo®, AST Farma BV, Oudewater, the Netherlands) vaporized in oxygen at concentrations of up to 5%.

Rats were implanted bilaterally with stainless steel guide cannulas (length: 5 mm; 22 ga; Plastics One type C313GRL, Plastics One Inc., Roanoke, VA, USA) using an in-house built stereotaxic model (Bayer Elberfeld Appnr. 159406; Tropon Inv. Nr. 36774). The cannulas were aimed at the prelimbic cortex under a lateral angle of 20° using the following coordinates adapted from the atlas of Paxinos and Watson (2005) to our rats: anteroposterior (AP): 10.46 mm (1.46 from bregma); mediolateral (ML): ±1.7 mm (from midline); dorsoventral (DV): −3.6 (flat skull). The AP coordinates were adjusted when necessary, i.e., when the distance between the interaural line and bregma deviated from the value of the atlas (9 mm). Stylets were inserted into the cannulas and remained in place until the infusions were made.

Elevated plus maze

The EPM was made of gray PVC and elevated 75 cm above the floor. The four arms (50 cm × 10 cm) formed a cross with the central platform. A wall (height: 30 cm) of non-transparent material enclosed two arms, located opposite to each other. Each rat was placed on the central platform facing one of the enclosed arms and allowed to freely explore the maze for 5 min. In between trials, the maze was cleaned with warm water and dried thoroughly using clean towels. Behavior was recorded on DVD and scored afterward using Observer 5.0 (Noldus Information Technology, Wageningen, the Netherlands).

Rodent Iowa Gambling Task

The same apparatus and procedure was used as previously described (Van den Bos et al., 2006b; Homberg et al., 2008; De Visser et al., 2011) with minor modifications, such as the number of trials per day (see below). The r-IGT apparatus was made of wood and consisted of a start box, choice area, and four arms. Before the start of testing, rats were habituated to the apparatus in a 10-min free exploration trial. Two days later, they were mildly food restricted (approximately 95% of free feeding body weight) and tested for a period of 9 days, i.e., a 5-day period and a 4-day period, interspersed by a two test free days (weekend days). Food was freely available on weekend days. A trial started by lifting the slide door of the start box. The rat could freely enter the choice area of the apparatus and choose one of the four arms. The chosen arm was only closed when the rat had entered a choice arm with its full body, including its tail. At the end of the arm, rats could obtain sucrose pellets or quinine-treated sucrose pellets (baited arms; see below) or no pellets at all (empty arms). Each trial had a maximum duration of 6 min. The inter-trial interval was 30 s. The rats received a total of 120 trials: 6 days of 10 trials, and 3 days of 20 trials. Intra-cerebral injections were given on the three sessions of 20 trials (see below). Rewards were 45 mg sucrose pellets (BioServe Inc., Frenchtown, NJ, USA) and punishments were quinine-treated sucrose pellets that were unpalatable but not uneatable. Most rats consumed the quinine-treated pellets once, but left them uneaten on subsequent encounters. Rats that consistently ate the quinine-treated sucrose pellets were excluded from the analysis. Of the four arms in the maze, two were baited and two were empty. The two empty arms were included to measure non-reward related exploration (Van den Bos et al., 2006b; Homberg et al., 2008; De Visser et al., 2011). The two baited arms consisted of a "bad" arm and

a "good" arm. In the "bad" arm, the rats received occasional big rewards (three sucrose pellets in 1 out of 10 trials) among frequent punishments (three quinine-treated sucrose pellets in 9 out of 10 trials). In the "good" arm, the rats received frequent small rewards (one sucrose pellet in 8 out of 10 trials) and infrequent punishments (one quinine-treated sucrose pellet in 2 out of 10 trials). This provided the same principle as in the human IGT: an option with a chance of a big reward (three sucrose pellets), but with little long-term success (three sucrose pellets per 10 trials; cf. decks A and B; Bechara et al., 1994) and an option with a chance of a small reward (one sucrose pellet), but with bigger long-term success (eight sucrose pellets per 10 trials; cf. decks C and D). The location of the baited and empty arms, as well as "good" and "bad" arms was counterbalanced across subjects.

Microinfusion procedure

The mPFC was bilaterally inactivated by infusion of a drug mixture containing the $GABA_A$ agonist muscimol (MSM; 0.1 nmol, Sigma-Aldrich, St. Louis, MO, USA) and the $GABA_B$ agonist baclofen (BAC; 1.0 nmol, Sigma-Aldrich) dissolved in saline and injected in a volume of 1.0 μL per side using a 26-ga injection needle protruding 0.5 mm past the end of the cannulas (Martin and Ghez, 1999; McFarland and Kalivas, 2001). Infusions were done using a device consisting of a 10-μL Hamilton syringe attached to tubing and the injection needle. Either the muscimol/baclofen mixture (MSM/BAC) or saline was injected by hand at a rate of approximately 0.5 μL/min. Rats were injected in a Makrolon type II cage, using a swivel allowing the animals to move freely during the procedure. The needle was left in place for an additional 1 min to allow for diffusion. Hereafter rats were returned to their home cage. After 15–20 min behavioral testing (EPM, r-IGT) started.

Rats were randomly allocated to the experimental groups: control rats received saline, while MSM/BAC rats received the mixture of GABA-agonists. Each rat received a single infusion prior to testing on the EPM. For the r-IGT, all rats were first trained for a total of 60 trials before receiving three daily infusions of either saline or MSM/BAC. After each infusion they received 20 trials, reaching a total of 120 trials by the end of the experiment.

Histology

After completion of behavioral testing rats were decapitated and the brains were quickly removed and frozen in liquid (−80°C) 2-methylbutane which was cooled with dry ice and stored at −80°C. Coronal sections (20 μm) were cut on a cryostat and mounted on Menzel SuperFrost Plus slides (Menzel GmbH & Co, Braunschweig, Germany) and stained with cresyl violet. Cannula placements were verified with reference to the neuro-anatomical atlas of Paxinos and Watson (2005).

BEHAVIORAL MEASURES

EPM measures

Behavior on the EPM was analyzed as in our previous study (De Visser et al., 2011). Based on the data analysis of that study, the following parameters were taken: time spent on the open arm, as a measure of anxiety, and the number of closed arm entries, as a measure of general activity. An arm entry was scored when the animals had at least three paws on the arm.

r-IGT measures

To determine the choice behavior of the rats, the number of visits to the "bad" or disadvantageous arm was calculated as a fraction of the total visits to the two baited arms. To measure choices for unrewarded arms, the number of visits to the empty arms was calculated as a fraction of the total number of trials per block. From trial block 41–60 onward clear differences begin to emerge between "poor performers" and "good performers" (see Figure 2, panel A: De Visser et al., 2011). Therefore, we used a split-median approach to differentiate "good performers" from "poor performers": subjects below the median were designated as "good performers," subjects above the median "poor performers." The performance in trial blocks 61–80, 81–100, and 101–120 was measured as per cent change from the respective base-line values at trial block 41–60. This split-median approach was done separately for empty arms and baited arms.

Responses to encounters with quinine-treated sucrose pellets or sucrose pellets in the advantageous arm were measured as win-stay/lose-shift behavior (see De Visser et al., 2011). As the number of visits to this arm may be low in animals treated with MSM/BAC in the mPFC the data were analyzed in one single trial block, i.e., trial block 61–120. Thus, when rats encountered a sucrose reward, its subsequent choice was scored as a win-stay when it revisited the advantageous arm. When rats encountered a quinine punishment, its subsequent choice was scored as a loose-shift when the rat switched to another arm. Win-stay and lose-shift was calculated as a fraction of the number of encounters with either sucrose pellets (win) or quinine-treated sucrose pellets (loss). Furthermore, the total number of switches between different arms was calculated as a measure of exploratory behavior (De Visser et al., 2011).

STATISTICAL ANALYSIS

All statistical analyses were carried out using SPSS 16.0 for Windows. For the EPM Student *t*-tests were performed to determine differences between the control and the MSM/BAC group on the time spent on the open arms and the number of closed arm entries. For the r-IGT a two-way analysis of variance (ANOVA) was run, with one factor encompassing treatment (saline versus MSM/BAC) and one factor as repeated measure (trial blocks 61–80, 81–100, and 101–120). This was done for the choices of both empty and baited arms. One sample *t*-tests were used to determine whether rats improved from base-line (trial block 41–60 = 100%). Student *t*-tests were used to assess significant differences between treatments (saline versus MSM/BAC) for the number of switches, win-stays, and lose-shifts.

Statistical significance was set at $p \leq 0.05$ (two-tailed); *p*-values ≤ 0.10 (two-tailed) were considered trends (*t*), NS: non-significant [$p > 0.10$ (two-tailed)].

RESULTS

GENERAL

Five rats ($n = 2$ MSM/BAC group, $n = 3$ saline group) were excluded from analysis due to incorrect placement of the cannulas or to not completing the IGT because of problems with cannulas. No rats were excluded for eating quinine pellets. This left $n = 25$ rats for data analysis.

INJECTION SITES

Figure 1 shows the location of tip of the cannulas. Injections were directed at the PrL of the mPFC.

ELEVATED PLUS MAZE

Due to a technical problem with the injection device (leakage), we lost one batch of rats ($n = 7$ animals), leaving 18 rats for further testing. Rats in the MSM/BAC group ($n = 10$) spent less time on the open arms of the EPM ($t = 3.508$, df = 16, $p = 0.003$) than rats in the saline group ($n = 8$; **Figure 2**). No difference existed regarding the number of closed arm entries ($t = -0.712$, df = 16, $p = 0.487$, NS). Thus, inactivation of the mPFC resulted in an increase in anxiety-related behavior without changes in general activity.

r-IGT PERFORMANCE

Good performing rats showed a lower fraction of visits to the disadvantageous arm (mean ± SEM: 0.25 ± 0.03; $n = 13$) than poor performing rats (0.52 ± 0.03; $n = 12$) at trial block 41–60. As can be seen in **Figure 3A**, saline-treated good performing rats improved in choosing the long-term advantageous arm from base-line in trial blocks 61–80, 81–100, and 101–120, while MSM/BAC-treated rats remained nearly at the same level of performance. Statistical analysis revealed a significant treatment effect in trial blocks 61–80, 81–100, and 101–120 [$F(1,11) = 5.665$, $p = 0.04$] but no interaction term [trial block * treatment $F(2,22) = 0.162$, NS]. In contrast, as can be seen in **Figure 3B**, both saline-treated and MSM/BAC-treated poor performing rats improved in choosing the long-term advantageous arm from base-line in trial blocks 61–80, 81–100, and 101–120. Statistical analysis revealed no significant differences between saline-treated and MSM/BAC-treated rats [trial block * treatment $F(2,20) = 0.460$, NS; treatment $F(1,11) = 0.101$, NS].

Good performing rats showed a lower fraction of visits to the empty arms (mean ± SEM: 0.24 ± 0.02; $n = 11$) than poor performing rats (0.46 ± 0.02; $n = 14$) at trial block 41–60. As can be seen in **Figure 3C**, neither saline-treated nor MSM/BAC-treated good performing rats improved in choosing baited over empty arms from base-line in trial blocks 61–80, 81–100, and 101–120. Statistical analysis revealed no significant differences between saline-treated or MSM/BAC-treated rats [trial block * treatment $F(2,18) = 0.559$, NS; treatment $F(1,9) = 0.008$, NS]. As can be seen in **Figure 3D**, both saline-treated and MSM/BAC-treated poor performing rats improved in choosing baited arms from base-line in trial blocks 61–80, 81–100, and 101–120. Statistical analysis revealed no significant differences between saline-treated or MSM/BAC -treated rats [trial block * treatment $F(2,24) = 0.458$, NS; treatment $F(1,12) = 0.715$, NS].

Tables 1 and **2** show that neither in good performing nor in poor performing rats differences occurred between saline-treated

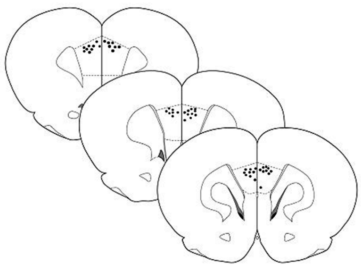

FIGURE 1 | Schematic drawing of coronal sections of rat brain showing the location of cannula tips used for micro infusions into the mPFC. Sections correspond to the atlas of Paxinos and Watson (2005).

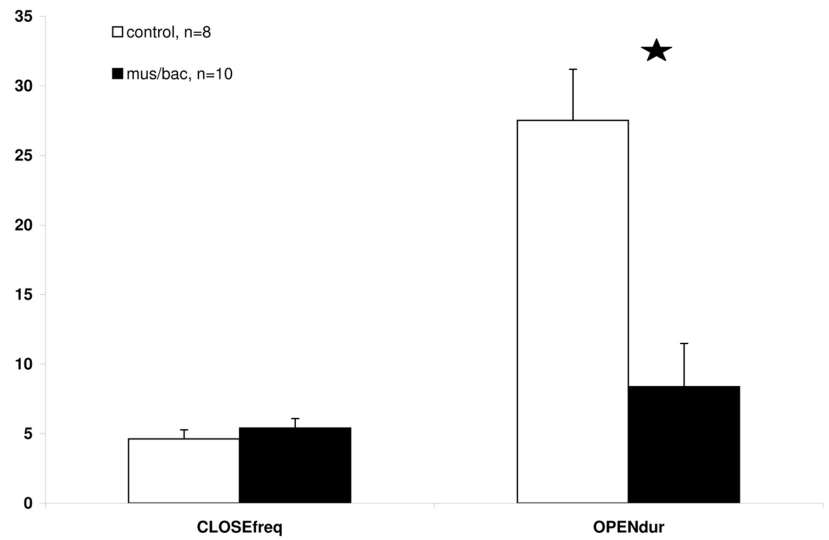

FIGURE 2 | Differences in EPM behavior between mPFC saline injected and MSM/BAC injected rats. CLOSEfreq = the number of closed arm entries, OPENdur = the time spent on one of the open arms as a percentage of total observation time. Shown are means ± SEMs, $*p \leq 0.01$ between groups.

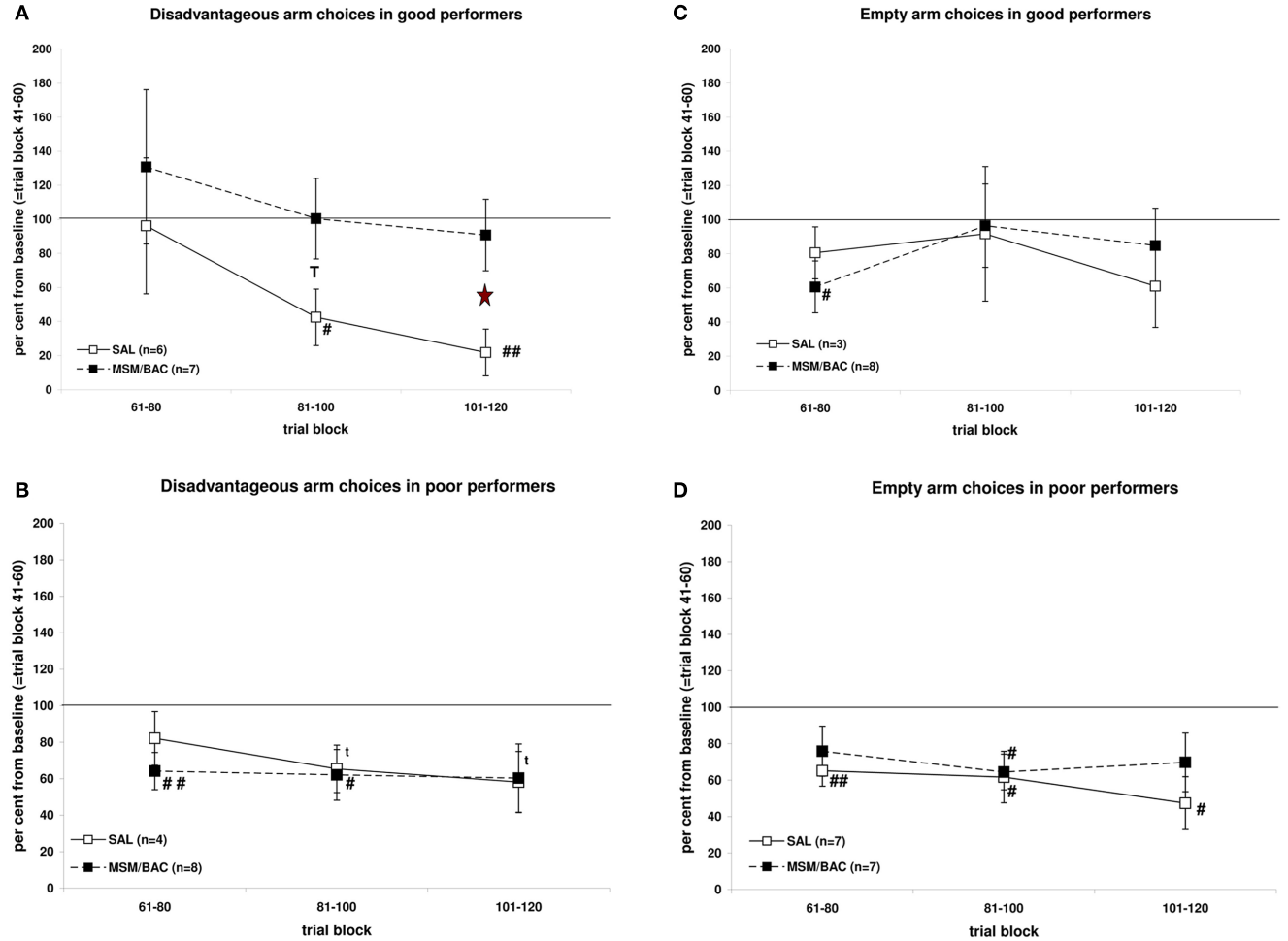

FIGURE 3 | Effects of injections of MSM/BAC or saline into the mPFC on r-IGT performance for the disadvantageous choices (A,B) and empty arm choices (C,D). Shown are means ± SEMs of per cent change from base-line (=trial block 41–60). *T*: $p \leq 0.10$ MSM/BAC *versus* saline; *: $p \leq 0.05$ MSM/BAC *versus* saline; *t*: $p \leq 0.10$ relative to 100%; #: $p \leq 0.05$ relative to 100%; ##: $p \leq 0.01$ relative to 100%.

Table 1 | Mean (±SEM) values of behavior related parameters for saline-treated and MSM/BAC-treated rats in trial block 61–120 in good performing animals (trial block 41–60).

Parameter	SAL ($n = 6$)	MSM/BAC ($n = 7$)
Switches	27.3 ± 3.0	28.9 ± 3.0
Win-Stay	0.63 ± 0.09	0.62 ± 0.06
Lose-shift	0.29 ± 0.09	0.26 ± 0.07

Table 2 | Mean (±SEM) values of behavior related parameters for saline-treated and MSM/BAC-treated rats in trial block 61–120 in poor performing animals (trial block 41–60).

Parameter	SAL ($n = 4$)	MSM/BAC ($n = 8$)
Switches	35.3 ± 2.1	34.8 ± 3.7
Win-Stay	0.51 ± 0.06	0.42 ± 0.10
Lose-shift	0.32 ± 0.11	0.50 ± 0.07

and MSM/BAC-treated rats regarding the number of switches, win-stay behavior or lose-shift behavior.

DISCUSSION

The present study yielded two main findings. Transient inactivation of the mPFC by injecting the GABA-agonists muscimol and baclofen (1) enhanced anxiety on the EPM, and (2) disrupted improvement of choosing the long-term advantageous option in the second part of the r-IGT in rats that already showed a good performance, but not in rats that showed a poor performance.

Our injection sites were mainly within the prelimbic area of the mPFC. However as we used an injection volume of 1.0 μL we probably also inactivated the underlying infralimbic area. However both structures are implicated in the relationship between anxiety and decision-making as exemplified from our earlier study (De Visser et al., 2011). Accordingly, we will refer to the mPFC in the remainder of the text.

Inactivation of the mPFC decreased the percentage of time spent on the open arms of the EPM, but did not affect the number of closed arm entries. Thus, levels of anxiety were increased after inactivation of the mPFC, but not levels of general activity. This finding is in line with the data of some studies which indicated that inactivation of the mPFC (PrL and/or IL) increased anxiety on the EPM (Silva et al., 1986; Jinks and McGregor, 1998), but not with those of others (Sullivan and Gratton, 2002; Shah and Treit, 2003; Davis et al., 2010; Stern et al., 2010). Although various reasons may underlie these differences between studies including the present study, such as different procedures used (permanent lesions versus transient inactivation, EPM protocols used, handling of animals), we show here that inactivation of the mPFC also hampered task-progression for choosing the best long-term option in the r-IGT in good performing rats as predicted from our earlier study (De Visser et al., 2011). Recent studies using the EPM, r-IGT, and c-fos expression confirmed the relationship between mPFC c-fos activity, r-IGT performance, and levels of anxiety in another strain of rats (Long Evans rats; Van Hasselt et al., in preparation). Overall, these data suggest that at least in our hands mPFC inactivation is associated with increased levels of anxiety.

The fact that we observed a selective effect – no effect on empty arm choices and only an effect within the baited arms in good performing rats – indicates that inactivation of the mPFC did no lead to general effects on working memory or attention, in which the mPFC has been implicated (Seamans et al., 1998; Vertes, 2006; Maddux and Holland, 2011; conform Enemoto et al., 2011). The mPFC was inactivated during the second part of the r-IGT. Analogous to the human IGT (Bechara et al., 1994), the rat task consists of two phases: initially, subjects gradually learn the contingencies of the advantageous and disadvantageous options by exploration, while during the later stages of the task they establish and express a preference for the advantageous option, and show a clear increase in the number of choices for that option, i.e., express task-learning. Indeed, as was suggested in earlier studies using this version of the IGT (Van den Bos et al., 2006b; Homberg et al., 2008; De Visser et al., 2011) the transition from exploration to establishing a long-term advantageous choice occurs during the second part of the task, i.e., after trial block 41–60. We have argued earlier that the mPFC becomes more involved as subjects express their preference for the best long-term option, while cortical structures such as the ventromedial prefrontal cortex/orbitofrontal cortex are more involved during the exploratory phase as subjects learn the overall reward value of the different options (Van den Bos et al., 2006a, 2007; Lawrence et al., 2009; De Visser et al., 2010, 2011). In line with this, the effect of mPFC inactivation on r-IGT performance was dependent on the level of base-line performance as we only observed effects in good performing rats, i.e., rats which showed a clear preference for the advantageous arm. The poor performing rats at trial block 41–60 improve their task performance, reflected by a decrease in the number of disadvantageous choices, irrespective of treatment. The good performing saline-treated rats still show an increased performance, while the MSM/BAC-treated rats did not show this improvement. These findings indicate that the activity of the mPFC may be critical in a window during decision-making where subjects have changed their behavioral strategy toward choosing the long-term advantageous option, i.e., shifting their behavioral strategy from exploration to exploitation.

The present data are therefore in line with a growing body of literature that the mPFC is critically involved in strategy shifting, behavioral flexibility, and goal-directed learning behavior by encoding task-rules (Dias et al., 1996; Ragozzino et al., 1999; Birrell and Brown, 2000; Floresco et al., 2008; Tran-Tu-Yen et al., 2009; Young and Shapiro, 2009; Balleine and O'Doherty, 2010; Sul et al., 2010). The functional integrity of the mPFC may allow for the coupling of the history of the choices of an animal and rewards (computation) as well as behavioral flexibility to generate and implement an optimal decision-making strategy under conditions of uncertainty. The present findings echo those of a recent study in which the mPFC was shown to be involved in proper performance in a probabilistic discounting task, which shares characteristics with the r-IGT (St Onge and Floresco, 2010). Interestingly, involvement of the mPFC in the human IGT has been especially associated with punishment processing (Lin et al., 2008) and risk anticipation (Fukui et al., 2005). In this scenario, the mPFC contributes to cognitive control over emotional influences on behavior, allowing the subject to maintain a long-term perspective and withhold responding to immediate rewards or losses (McClure et al., 2004; Tanaka et al., 2004).

In our earlier study we observed that the good performing – low anxious rats were characterized by a decrease in the overall number of switches, and a strong increase in win-stay behavior, and strong decrease in lose-shift behavior in the advantageous arm, while poor performing – high anxious rats were characterized by an overall high number of switches, and a weak increase in win-stay behavior, and weak decrease in lose-shift behavior in the advantageous arm (De Visser et al., 2011). Accordingly, these data suggested that poor performing – high anxious rats remained exploratory and responsive to for instance immediate losses in contrast to good performing – low anxious rats. Here we show that the effects of mPFC inactivation did not completely mirror our earlier findings: we did not observe an effect on switches, win-stay, and lose-shift strategies. However it should also be noted that differences between good performing – low anxious rats and poor performing – high anxious rats were not solely related to differences in c-fos expression in the mPFC (PrL and IL) but also to differences in the core and shell of the nucleus accumbens (De Visser et al., 2011). More specifically, poor performers showed an increased level of c-fos expression in the nucleus accumbens shell compared to good performers, while increased levels of neural activity in the nucleus accumbens core were found in good performers compared to poor performers. This implies also a crucial role for the nucleus accumbens in regulating both decision-making and anxiety (conform Lopes et al., 2007; da Cunha et al., 2008). To what extent therefore differences in switches, win-stay, and lose-shift behavior, that underlie or are related to differences in overall IGT performance between individuals are specifically associated with differences in the *interaction* of cortical (mPFC) and subcortical (nucleus accumbens;

Yin et al., 2008; see also De Visser et al., 2011) structures remains to be determined.

It should finally be noted that given the small number of rats the results are still preliminary. However, the present data contribute to understanding the role of prefrontal areas in performing the r-IGT and complement recent lesion-studies on the role of prefrontal areas in the r-IGT (Rivalan et al., 2011; Zeeb and Winstanley, 2011). In these studies the mPFC (PrL) was also implicated and suggested to play a role in detecting action–outcome contingency variations, i.e., conditions of uncertainty, leading to an inability to change behavior when lesioned, i.e., perseverative responding (Rivalan et al., 2011).

CONCLUSION

The data of this study suggest that impaired function of the mPFC may be one factor leading to both high anxiety and poor decision-making.

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Mapping spikes to sensations

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Single-unit recordings conducted during perceptual decision-making tasks have yielded tremendous insights into the neural coding of sensory stimuli. In such experiments, detection or discrimination behavior (the psychometric data) is observed in parallel with spike trains in sensory neurons (the neurometric data). Frequently, candidate neural codes for information read-out are pitted against each other by transforming the neurometric data in some way and asking which code's performance most closely approximates the psychometric performance. The code that matches the psychometric performance best is retained as a viable candidate and the others are rejected. In following this strategy, psychometric data is often considered to provide an unbiased measure of perceptual sensitivity. It is rarely acknowledged that psychometric data result from a complex interplay of sensory and non-sensory processes and that neglect of these processes may result in misestimating psychophysical sensitivity. This again may lead to erroneous conclusions regarding the adequacy of candidate neural codes. In this review, we first discuss requirements on the neural data for a subsequent neurometric-psychometric comparison. We then focus on different psychophysical tasks for the assessment of detection and discrimination performance and the cognitive processes that may underlie their execution. We discuss further factors that may compromise psychometric performance and how they can be detected or avoided. We believe that these considerations point to shortcomings in our understanding of the processes underlying perceptual decisions, and therefore offer potential for future research.

Keywords: psychophysics, perception, signal detection theory, psychometric, neurometric, receiver operating characteristic, psychophysical task, single-unit electrophysiology

INTRODUCTION

Gustav Theodor Fechner is best known as the founding father of psychophysics. It is perhaps less well known that Fechner distinguished between what he called "outer psychophysics", the relationship between physical stimuli and sensation, and "inner psychophysics", the relationship between (neuro-) physiological activity and sensation. While being successful at making outer psychophysics the cornerstone of the evolving science of psychology, physiological methods at his time were not developed enough to allow direct investigation of inner psychophysics, and Fechner was well aware of this limitation (Fechner, 1860; Baird and Noma, 1978).

This situation has changed dramatically in the meantime, mainly with the advent of the awake behaving monkey preparation (Evarts, 1966), which allows for the simultaneous assessment of psychophysical measurements (psychometric data, e.g., percent correct responses) and spikes from (mostly cortical) single neurons in sensory areas of the brain (neurometric data; e.g., Newsome et al., 1989; Mountcastle et al., 1990; Vogels and Orban, 1990). These seminal studies, as well as a multitude of studies published since then, have centered around neurometric–psychometric (NP) comparisons in the sense that some measure of performance quality (such as a detection threshold or a difference limen) is extracted from the neuro- and the psychometric data for direct comparison on the same scale (reviewed in Parker and Newsome, 1998). In concert with the application of signal detection theory (SDT, Green and Swets, 1966) to neurometric data, these studies have provided striking evidence that the stimulus detection and discrimination capacity of single sensory neurons can be close to or even exceed the capacity of the entire organism. These findings are in agreement with Barlow's (1961) notion of redundancy reduction: Barlow postulated that the neuronal representation of stimulus information (i.e., the representation relevant for Fechner's inner psychophysics) must be efficient (Barlow, 1961, 1972); in other words, as few spikes as possible in as few neurons as possible should be used to encode a sensory stimulus, a tenet quite different to Sherrington's (1940) idea of the brain as "a million-fold democracy", in which each citizen (neuron) counts for little.

The NP comparison has realized Fechner's dream of "inner psychophysics" – relating neurophysiological activity to sensation. However, the precise nature of this relationship is still far from clear. There are a variety of unresolved questions, among them:

(1) What is the role of single neurons in the representation of information? This question is closely related to the discriminability of a given set of stimuli by single neurons' responses.

Whether a neuron's discriminability is to be considered high or low can be most meaningfully assessed if viewed relative to psychophysical performance (Stüttgen, 2010). High discriminability of single neurons is a prerequisite for sparse coding; thus, it can constrain theories on how information is represented in a given brain area (such as response pooling or the lower envelope principle; Parker and Newsome, 1998). This, in turn, relates closely to Barlow's (1972) notions about the efficiency of neuronal representations.

(2) What neural code is used for stimulus representation? NP comparisons can be used to compare psychometric to neurometric performance based on different candidate codes. For instance, it has been found that two candidate codes, firing rate and firing periodicity, both carry ample information about vibrotactile stimuli (Hernandez et al., 2000; Arabzadeh et al., 2006). The code with a neurometric performance that best matches the performance of the observers is then typically assumed to be the one that is used by the brain (e.g. Salinas et al., 2000; Luna et al., 2005). More systematic approaches try to assess "complete" neuronal populations (see below) and pit candidate codes against each other. Whenever some code's performance, computed in a statistically optimal fashion, falls short of the subjects' psychometric performance, that neuronal code can be rejected (Jacobs et al., 2009).

(3) How is sensory information exploited for perceptual decision-making? Aside from the question of sensory processing, perceptual decision-making encompasses the problem of how sensory information is put to use for adaptive action (Gold and Shadlen, 2001, 2007). For example, monkeys do not make use of all stimulus information available to them, but rather commit to action prior to stimulus termination, thereby ignoring useful information (Roitman and Shadlen, 2002; see also Resulaj et al., 2009). Also, psychophysical performance is frequently not solely determined by sensory processes but by a range of biasing factors, among them recent stimulus and reward history (Boneau et al., 1965; Busse et al., 2011).

Importantly, the validity of claims about coding schemes on the single-neuron and population level hinges crucially on the precise assessment of the sensory limits of the observer, i.e., psychophysical sensitivity. While great effort has been devoted to the study of neural coding at both the level of individual neurons and neural populations (e.g., Bialek et al., 1991; Shadlen et al., 1996; de Ruyter van Steveninck et al., 1997; Riehle et al., 1997; Gold and Shadlen, 2007; Jacobs et al., 2009), we believe that research aimed at the understanding of the cognitive processes underlying performance in a given psychophysical task has been comparatively neglected by the community. As we will argue below, this could have led to a systematic underestimation of psychophysical sensitivity of animal subjects and, consequently, to an overestimation of neurometric relative to psychometric sensitivity.

In the remainder of the article, we will first review problems in acquiring neurometric data suitable for NP comparisons, a prime focus of research in the last 20 years. Then, turning toward the problem of measuring the psychometric function, we will introduce signal detection theoretical "process models", i.e., models of the sequence of cognitive steps underlying performance in these tasks. We will discuss additional factors affecting psychophysical performance not accounted for by such process models. We argue that, in order to gain further insight into the physiology of perception, the entire cascade of cognitive processes underlying perceptual decision-making tasks has to be explored.

ESTIMATING NEUROMETRIC SENSITIVITY

Conducting an NP comparison poses two distinct problems: the assessment of neurometric sensitivity and the assessment of psychometric sensitivity. In this section, we will first briefly introduce what is meant by an NP comparison. Then, we will discuss problems that arise when attempting to determine psychometric sensitivity.

Figure 1 illustrates a simple NP comparison for a yes/no detection task. Several stimuli whose intensities are distributed around the presumed absolute threshold of detectability are presented

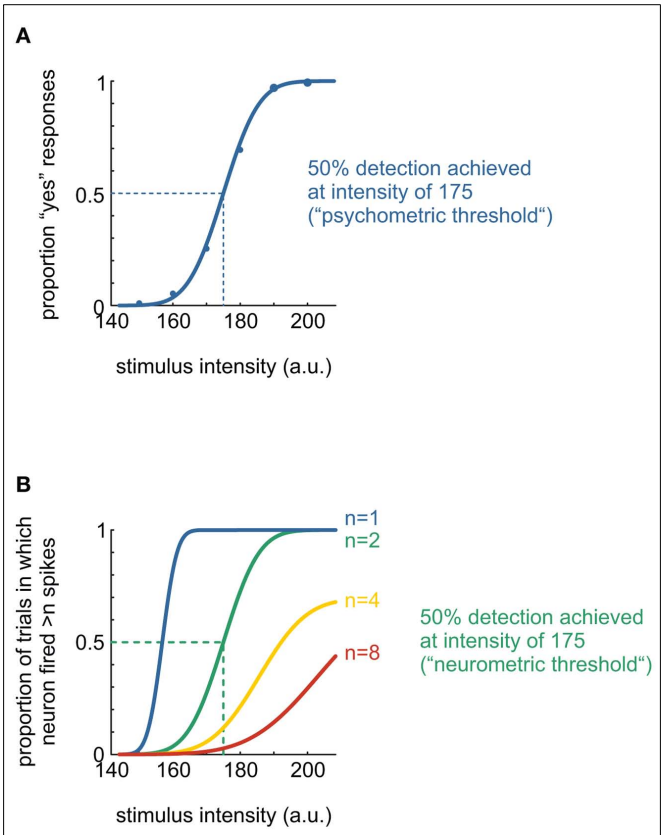

FIGURE 1 | Example illustration of a neurometric–psychometric comparison. (A) A typical psychometric curve from a yes/no detection experiment with six stimuli of varying intensity (see **Box 1**). Smooth line indicates fit of a cumulative Gaussian to the data points. Dotted line indicates the stimulus value at which the psychometric curve reaches 50% of its final height. This value is commonly taken as the psychophysical threshold. **(B)** Some typical neurometric curves: a single neuron's spikes were counted during stimulus presentation. The neuron was assumed to "detect" the event when it fired in excess of *n* spikes during stimulus presentation, where *n* here encompasses 1, 2, 4, and 8 spikes. The neurometric curve for $n = 2$ matches the psychometric curve best, as assessed by their common threshold of 175 (arbitrary units). Thus, the NP ratio here is $175/175 = 1$.

many times to an observer, whose task is to respond "yes" if he perceives the stimulus and "no" otherwise. As stimulus intensity increases, the proportion of "yes" responses increases as well. The pattern of responses can be fitted by a sigmoidal function. The resulting psychophysical curve is characterized by at least two parameters, the threshold (the point on the abscissa corresponding to 50% detection performance) and the slope of the curve. The term "psychophysical sensitivity" refers to the reciprocal of threshold; thus, the lower the threshold, the higher the sensitivity.

Imagine that, while the observer was performing the task, a sensory neuron of his is recorded, and its spike responses during stimulus presentation are counted. Neurometric curves can be constructed in a simple way by determining the proportion of stimulus presentation trials on which the neuron fired more than n spikes (i.e., the neuron is deemed to detect the event when more than n spikes are fired during stimulus presentation). **Figure 1B** displays the results of this exercise for n comprising 1, 2, 4, and 8 spikes. It is readily visible that the curve constructed with a criterion of $n = 2$ resembles the psychometric curve best in terms of both threshold and slope. In fact, psychometric and neurometric threshold (for $n = 2$) are identical in this example, and the NP ratio therefore equals 1. Of course, there are considerably more ways to construct neurometric curves, perhaps most notably receiver-operating characteristic (ROC) analysis (Vogels and Orban, 1990; Britten et al., 1992), which compares distributions of spike counts for pairs of stimuli and returns the maximum classification performance. There exists a variety of population coding schemes beyond simple spike counts, involving spike timing, spike correlations within (Jacobs et al., 2009), and between spike trains of different neurons (Zohary et al., 1994; Shadlen et al., 1996; Schneidman et al., 2006; Shlens et al., 2006, 2009; Ohiorhenuan et al., 2010).

Obviously, NP comparisons require two different kinds of measurement – estimating psychometric and neurometric sensitivity. We will have more to say about psychometric sensitivity below. For now, we focus on two important preconditions for the assessment of neurometric sensitivity: causality and completeness. Naturally, in order to make meaningful NP comparisons, the sensory neurons under investigation must be involved in the psychophysical task at hand, i.e., neural activity of these neurons must be causally related to psychophysical performance. The neurometric signals entering the NP comparison should be necessary and, ideally, also sufficient to explain the sensory-driven aspects of the behavior. This requires to record from an "informational bottleneck", i.e., a neural structure through which all relevant signals pass and which does not receive feedback signals from downstream structures. This way, a clear identification of cause and effect is possible. Unfortunately, such informational bottlenecks are rarely to be found, one notable exception being retinal ganglion cells (Jacobs et al., 2009). In the central nervous system, the direction of signal flow in ascending sensory pathways is ambiguous. With very few exceptions, subsequent levels of processing are interconnected in a bidirectional way. Also, circular connectivity often bypasses stations on the ascending pathways (e.g., cortical feedback of brain stem centers bypassing thalamic stations; Furuta et al., 2010). These problems exacerbate in the neocortex where neurons are intricately interconnected – to their neighbors as well as to a multitude of distant neurons residing in other areas. Thus, a close look at the detailed connectivity of sensory systems blurs the notion of an "ascending pathway." Instead, sensory systems seem to be described better as complex networks, which receive signals at one point and output signals at another with reverberating signal flow in-between. In conclusion, informational bottlenecks, furnishing completeness, and causality, are difficult to define in the central nervous system. Alternatively, a causal contribution of a neuronal structure can be demonstrated by showing that the behavior is blocked/evoked by lesions/electrical stimulation of the structure in question (Parker and Newsome, 1998). A cautionary note is in order, however, as psychophysical performance can readily be impaired by blocking structures located downstream from the ones actually performing the critical (sensory) computation; in this case, performance degradation may be due to, e.g., response confusion rather than abolition of the sensory function proper. Furthermore, abolishment of a function may result from disrupting non-specific modulatory structures with no contribution to encode or compute the concrete signals under observation. Also, parallel processing of sensory information along a different sensory pathway cannot be ruled out by this strategy; in the latter case, psychometric performance would depend on two or more structures, and the relation between neurons and sensation cannot be pinned down since the relative importance of the structures is not known.

Yet another strategy is to artificially "create" informational bottlenecks by presenting point-like stimuli in both space and time (Hecht et al., 1942; Barlow, 1961; Sakitt, 1972; Johansson and Vallbo, 1979; Vallbo et al., 1984). Point-like stimuli are attractive for studies of the physiology of perception as they reduce the number of neurons engaged in the task and the time window in which neuronal responses need to be monitored to a well specified minimum. Sakitt (1972), for instance, carried this strategy to the extreme as she studied the difference in visual detection performance evoked by just one photon more. One photon will interact just with one molecule of rhodopsin located in just one photoreceptor. This approach therefore ingeniously related the concept of informational bottleneck to just one cell in the layer of photoreceptors. Using sophisticated psychophysical techniques in humans, Sakitt successfully related a stimulus of "one more photon" to a difference in the subject's performance, and was thus able to conclude that the action of a single photoreceptor has a significant contribution to perception. A related concept is the attempt to electrically stimulate a single neuron, which has been first realized using electrical stimulation of individual primary afferent fibers in humans (Ochoa and Torebjork, 1983; Vallbo et al., 1984). These authors found that subjects perceived the activation of individual tactile nerve fibers in three out of the four classes of fiber types investigated. Some rapidly adapting fibers seem to give rise to a perceptual change with a difference of just one evoked spike. More recently, the technical advent of juxtacellular stimulation made this approach available for the study of the central nervous system (Houweling and Brecht, 2008; Voigt et al., 2008). Injecting just about 15 spikes in one neuron in primary somatosensory cortex evoked a measurable difference in detection performance of

a rat showing that even single cortical neurons can have an effect on perception. This method bears great promise to be used for systematic mapping of behavioral effects in different stations of a sensory pathway.

Unfortunately, single neuron responses (and thus artificial bottlenecks) cannot be realistically obtained with natural sensory stimuli evolving in space and time, at least in mammalian brains. Even limiting the stimulus in space and time and applying near-threshold intensities, not one but many neurons in primary sensory cortices will get activated (de Lafuente and Romo, 2005; Stüttgen and Schwarz, 2008, 2010). Thus, neither the assessment of a complete informational bottleneck (aside of retinal ganglion cells), nor the creation of an artificial one constituted by a single cell seems attainable. One study in the whisker-related primary somatosensory (barrel) cortex of rats has provided a quantitative hint on the number of neurons engaged vs. the number of neurons needed to match the perceptual performance. Using transient single-whisker deflections at psychophysical threshold, around a third of the stimulations at psychophysical threshold intensity were responded by neurons in the principal barrel cortical column of the stimulated whisker (Stüttgen and Schwarz, 2008). Thus, alone in the barrel column receiving strongest input of the stimulated whisker (the principal barrel column) around 3000 neurons are active with minimal stimulation. The number of all cells engaged in primary somatosensory cortex is surely far higher because cells in adjacent barrel columns respond as well to single whisker stimuli. On the other hand, the same study found that five of the most sensitive neurons carry sufficient information to explain the psychometric performance. In case the read-out mechanism is less selective, around 16 barrel cortex neurons might be sufficient. In fact, this discrepancy of thousands of cells engaged by the stimulus vs. a few needed to do the job has become a common theme in all studies trying to compare the performance of single neurons to the one of the subject. Since the pioneering studies of Newsome, Movshon, and coworkers in the late 1980s, the single neuron neurometric performance has been found with few exceptions to be close and somewhat lower compared to that of the observer (Tolhurst et al., 1983; Newsome et al., 1989; Britten et al., 1992; Geisler and Albrecht, 1997; Uka and DeAngelis, 2003; Purushothaman and Bradley, 2005; Stüttgen and Schwarz, 2008; Cohen and Newsome, 2009).

An outlier result were the findings of the pioneering studies (Britten et al., 1992; Celebrini and Newsome, 1994), as neurometric sensitivity was judged up to 10 times higher than the psychometric one. However, this estimate of neurometric sensitivity has been recently adjusted downward by showing that monkeys use only the first few hundred milliseconds of a stimulus, while the neurometric integration time in the original study extended to the full stimulus presentation of 2 s. Thus, the neurons were unfairly favored in the earlier study (Cohen and Newsome, 2009). In addition, it needs to be pointed out that these pioneers actually based their estimate of the neurometric sensitivity on *two* neurons, and not (as is often falsely understood) on a single neuron. The neurometric sensitivity was calculated from the measured neuron (selected to display high directionality), combined with a virtual one, the "antineuron", with opposite direction selectivity but otherwise identical response properties. In fact, the task to discriminate two stimulus directions does not fit well the properties of a single MT neuron, which, due to its high directional selectivity, is limited to convey information about the presence of a stimulus in a single preferred direction, and largely ignores the presence of stimuli in other directions. As a consequence, single MT neuron discriminability to two opposite directions is presumably far lower than claimed in the original study (Britten et al., 1992). Notably, other studies with the neurometric analysis strategy of postulating antineurons also found considerable fractions of neurons whose sensitivity exceeded that of the observer (MT: Uka and DeAngelis, 2003; MST: Heuer and Britten, 2004). A perhaps more suitable psychophysical task to probe the sensitivity of MT neurons would be the detection of movement direction along the neuron's preferred axis vs. zero net motion, which to our knowledge has not been tried so far. These points hardly diminish the impact of these landmark studies, but they suggest the view that single MT cells are likely to fall in line with neurons in many other sensory areas investigated since then, showing neurometric sensitivities to be somewhat lower than psychometric sensitivity.

With the common finding of NP sensitivity ratios of close to 1 but not exceeding it, it is typically very easy to combine neurometric performance of far fewer neurons than the number suspected (or known) to be engaged in the task to exceed the performance of the subject. Popular responses to this problem have been to postulate (i) sources of noise in downstream processing, (ii) detrimental effects introduced by neuronal correlations, or (iii) intricacies of read-out mechanisms. Despite their value as testable hypotheses, these possibilities must be deemed highly under-constrained without a direct assessment of the complete neuronal population, even though some of them – such as neuronal correlations – have received experimental support (Zohary et al., 1994; Cohen and Newsome, 2008).

In conclusion, future NP comparisons are likely to go beyond measurements of spike counts from single units with the aim to identify neuronal population codes. To do this, informational bottlenecks must be studied. The only attainable complete bottleneck in the central nervous system is the population of retinal ganglion cells, which should be further exploited for this purpose. In the peripheral nervous system, somatosensory afferents are equally attractive. Artificial bottlenecks must be extended to activity that evolves in space and time to identify neuronal activity leading to more complex perception. Juxtacellular stimulation of single neurons can be employed to systematically test activity varying over time (Houweling et al., 2010). Optogenetic approaches, which already allow to interfere with a genetically targeted population of cells, are a promising new tool to achieve this goal with amazing spatiotemporal precision (Yizhar et al., 2011), even in non-human primates (Diester et al., 2011).

ESTIMATING PSYCHOMETRIC SENSITIVITY

Sensations are not directly observable in the laboratory. Instead, the subject in a psychophysical experiment (observer) is asked to produce different responses contingent on particular aspects of his sensations. This could be the mere presence or absence of a sensation (stimulus detection), whether two stimuli are perceived to be different (stimulus discrimination), whether a stimulus is a specific one in a set of candidates (identification), or whether

a given stimulus belongs to a specific category of stimuli (categorization). In the early days of psychophysics, the behavioral response was simply seen as the effect of a stimulus once its intensity exceeded a sensory threshold. The threshold could be estimated by varying the stimulus intensity and measuring the percentage of correct responses (**Figure 1A**). However, psychophysical findings varied considerably both across tasks and across laboratories, prompting psychophysicists to develop more reproducible methods (Blackwell, 1952; Swets, 1961a,b; Swets et al., 1961). The decision-theoretic stance of SDT (Green and Swets, 1966) alerted experimenters to the fact that psychophysical measurements hinge crucially on non-sensory factors, among them prior probabilities, payoffs, and task strategy, thus recognizing the active role of the observer. Importantly, SDT's main index of psychophysical sensitivity (d') promised improved replicability of results across both tasks and laboratories. The ensuing success of SDT yielded a sharp increase in the use of its concepts, such as ROC analysis, across various fields of research (Swets, 1973). The power of these ideas is reflected also in the measurement of neurometric data. When comparing them to psychometric data, neurometric discriminability is often measured by ROC analysis (Vogels and Orban, 1990; Britten et al., 1992, 1996; Parker and Newsome, 1998). If decisional factors play a role for the behavioral response in psychophysical tasks, it is reasonable to deploy their manipulation for the study of perceptual processes. As a consequence, the focus in the last decade has shifted away from neuronal sensitivity toward the study of perceptual decision-making. It is now asked how and to what degree sensory representations also reflect the behavioral choice (Britten et al., 1996; Romo and Salinas, 2003; Gold and Shadlen, 2007; Nienborg and Cumming, 2009, 2010). A more recent development has been to go beyond varying stimulus parameters and explicitly vary payoffs and/or the frequency of the stimuli to study directly how representations of stimulus and choice correspond and interact (Feng et al., 2009; Rorie et al., 2010; Teichert and Ferrara, 2010; Stüttgen et al., 2011).

Despite these developments, the psychophysical task – at least when used to measure neuronal sensitivities – has, by and large, been considered merely a means to measure responses. Typically, the minimization of extra-sensory factors is considered as a given. Against the backdrop of the insights gained by SDT half a century ago about the psychological nature of even the simplest sensory detection tasks, it gives cause of concern how little possible effects of extra-sensory factors on the psychometric curve are discussed. Our goal in this review is to remind the reader that all parameters of the psychometric curve depend on the detailed procedure and will, thus, significantly affect the estimation of psychometric sensitivity and thereby the NP ratio. Each psychophysical task comes with different memory requirements, constraints on information processing, and effects on motivation and bias that limit the use of sensory information. In order to study how sensory information processing works – even at the sensor level – ultimately these more "psychological" factors have to be taken into account. We will start with a brief review of SDT and an analysis of cognitive processes underlying performance in commonly employed psychophysical tasks. Then, we will discuss additional non-stimulus factors outside the SDT framework that may significantly influence the subject's responses.

SDT ANALYSIS OF THE YES/NO TASK

The vast majority of researchers undertaking the NP comparison employ Go–NoGo (GNG), yes/no (YN), or Forced-Choice (FC) tasks (see **Box 1**, **Table 1**, and **Figure 2** for brief descriptions of these and some other psychophysical tasks). SDT offers a broad conceptual framework for the analysis of different psychophysical tasks. Here, we will illustrate SDT concepts mainly with YN and FC. The interested reader is referred to MacMillan and Creelman (2005) for further paradigms and discussion.

Signal detection theory starts with the assumption that each presentation of a signal yields a variable internal representation on a hypothetical decision axis. Similarly, even in the absence of sensory input, the system generates a non-zero, somewhat variable response. In the simplest and most widely used case, the distributions of the internal representation of both stimulus (S) and noise (N) are assumed to be normal and their variances identical (**Figure 3**).

The task can be conceptualized as a statistical decision problem. The observer is assumed to partition the decision axis into the discrete response options that are available to him: "yes", a signal was present, and "no", no signal was present (a similar logic applies to discrimination tasks). On each trial, there are four possible outcomes: (1) a signal is presented, and the observer responds "signal" (hit), (2) a signal is presented, and the observer responds "no signal" (miss), (3) no signal is presented, and the observer responds "signal" (false alarm), and (4) no signal is presented, and the observer responds "no signal" (correct rejection). Cases 1 and 4 are correct responses; cases 2 and 3 are false. Given this experimental setup, a payoff matrix assigns a value to each of the four possible outcomes. Usually, correct responses are equally likely to yield reinforcement, and reinforcers are of the same magnitude for cases 1 and 4. Incorrect responses are usually punished, and again punishments are of the same magnitude for cases 2 and 3. If this is the case, and the stimuli are equally likely to occur, the observer's optimal (in the sense of maximizing accuracy, and therefore expected payoff) decision criterion is located right in the middle between the two stimulus distributions. Thus, the probability of hits equals that of correct rejections, and the probability of false alarms equals that of misses. The discriminability of the two stimuli, N and S, is given by the difference of means of the two stimulus distributions on the decision variable, divided by the common standard deviation (SD) of the distributions. This measure is called d'. SDT separates sensory discriminability (indexed by d') and response bias, which is the distance of the decision criterion from a neutral position (a measure called c), and therefore, at least in theory, provides a measure of sensitivity untainted by response bias. This separation is of great value because the usual index of performance in psychophysics, percent correct, is known to be highly susceptible to variations in task structure and response bias (Green and Swets, 1966).

SDT ANALYSIS OF THE TWO-INTERVAL FORCED CHOICE TASK

A classic example for how SDT can help relate different psychophysical tasks is the relationship between YN and two-interval forced choice (2-IFC; the same applies to spatial two-alternative forced choice, 2-AFC). In a simple instantiation of 2-IFC, the

Box 1 | Description of psychophysical tasks

Go–NoGo (GNG)
The observer has one response option *R* available (e.g., pressing or releasing a lever, performing a nose poke, or pecking a response key) and is required to respond when a stimulus of class A is presented and not to respond when a stimulus of class B is presented. The outline of a typical trial is depicted in **Figure 2A**. After an inter-trial interval (ITI), a stimulus is presented. If the subject responds within a given time frame (the "response window") after target onset, reward is delivered; in case of a response after a non-target stimulus, punishment is delivered.
The biggest advantage of the GNG method is its simplicity. Animals are easily trained on GNG using intense, suprathreshold stimuli. Consequently, the intensity difference between the stimuli in classes A and B is gradually reduced, until no further improvement is possible (see Schwarz et al., 2010, for a methods review). Then, presenting a pseudorandom sequence of several stimuli ("method of constant stimuli"), the response probability for each stimulus is recorded, and a psychometric curve can be constructed (detection: Stüttgen et al., 2006, discrimination: Gerdjikov et al., 2010).
Note that this description refers to an instantiation of the yes/no task (a single stimulus per trial) in the form of a Go–NoGo paradigm. Of course, GNG can also be conducted with two stimuli per trial as in two-interval forced choice (see below).

Yes/no (YN; also known as A Not-A or single-interval forced choice)
The observer has two response options R_A and R_B available and is required to respond with "R_A" when stimulus A is presented and with "R_B" when stimulus B is presented. Rather than two individual stimuli, A and B can be classes of stimuli, e.g., leftward and rightward motion of various strengths. The outline of a typical trial is depicted in **Figure 2B**. After an inter-trial interval (ITI), a stimulus taken from either class A or class B is presented. If the observer emits the appropriate response within a given time frame (response window), reward is delivered; if the incorrect response is emitted, the subject is punished, usually by a brief time-out. In many monkey studies, the response consists in making a saccade to one of two choice targets. The term "yes/no" derives from main usage of the paradigm in studies of stimulus detection in the early days of psychophysics. However, use of the YN method is not limited to detection but is employed in studies of discrimination performance as well. Notably, many neuroscience papers list this paradigm as a "forced-choice task" (e.g., Britten et al., 1992), or "two-choice task" (Kepecs et al., 2008). Sometimes the YN-method is referred to as "single-interval forced choice." Although this terminology has some conceptual appeal, we will avoid this term lest we add to the terminological confusion. Note that, in signal detection theoretical contexts, the YN method is typically understood to employ only two stimuli per block of trials (the consequences of departure from this rule are discussed in the main text). In addition, psychophysicists sometimes refer to a yes/no task with more than two stimuli as the "method of single stimuli." Here we will use the term "yes/no task" for any task in which a single stimulus is presented per trial and in which the subject has two response options available, regardless of the total number of stimuli in the stimulus set.

Yes/no with reference (YNR)
This method is similar to the yes/no task described above with two different stimuli per trial. On each trial, a reference stimulus is presented first; then, a second stimulus (target) is presented. The subject's task is to judge whether the target stimulus is more or less intense than the reference stimulus along some sensory continuum. The rationale in using YNR is to avoid decrements in performance due to bad recall of the reference stimulus' features (stimulus uncertainty; see, e.g., Hautus et al., 2009).

Identification
The subject is presented with one of *m* stimuli in a single interval and has to emit one of *m* possible responses. Hence, the yes/no method with two stimuli is a special case of an identification task with only two responses. In cases where there are two responses which are not thought of as literally "yes" and "no", such as leftward vs. rightward motion, identification might be a better term than YN.

Same-different
The observer is presented with two stimuli, either simultaneously or in succession, and has to judge whether they are the same or different. The position or the sequence of the two stimuli in a pair is randomized. Unlike YNR, the first stimulus in this task is not identical across trials.

Forced Choice
This task can take many forms. In the most common application (the "*n*-interval forced choice task", *n*-IFC), there are *n* stimuli on each trial, and the observer has to choose a target out of $n-1$ distractor stimuli. In tactile psychophysics, a common implementation is the two-interval forced choice task (2-IFC, e.g., Luna et al., 2005; **Figure 2C**). Here, a stimulus is presented for a brief interval of time (e.g., 1 s), which is followed by a short inter-stimulus interval, and the presentation of a second stimulus. The subject has to decide which of the two stimuli the target is (e.g., which stimulus is of larger intensity or higher frequency). If 2-IFC is used to assess detection performance, one of the stimuli is the null stimulus, the other one is the target. Another implementation of forced choice is the spatial *n*-alternative forced-choice method (*n*-AFC, **Figure 2D**): on each trial, *n* stimuli are presented on a screen in front of the subject, who has to pick the target stimulus (e.g., Jacobs et al., 2009; see also Jäkel and Wichmann, 2006).
Incidentally, FC can also be instantiated as a GNG task, e.g., by asking the subject to respond when it believes the first stimulus to be the target, and to withhold responding when it believes otherwise.

A note on terminology
It is important to note the discordant uses of psychophysical terms in the animal neuro-psychophysics and the psychological literature. In forced choice methods (psychological use), the observer is always presented with multiple stimuli per trial, either in temporal succession (*n*-IFC) or simultaneously (e.g., at different spatial locations, *n*-AFC). An inconsistency of this terminology is that YN tasks are not commonly called FC, although they do feature a forced choice component (they require the observer to emit one of two responses on each trial). This is probably the reason why animal studies often call YN tasks FC, bearing the danger that characteristics of the different tasks that critically relate to the comparison of neurometric and psychometric data slip out of focus and get neglected (see main text). Here we adopt the psychological terminology (which is consistent with signal detection theory, see also Section 2.3.5 in Kingdom and Prins, 2010), despite the mentioned inconsistency; accordingly, many of the paradigms called "forced choice" in the neuroscience literature are referred to as yes/no method in the present review.

Table 1 | Overview over the most frequently used tasks in animal psychophysics and their properties.

	Number of stimuli per trial	Number of response options	Working memory for stimulus required?	Susceptibility to bias			Example for a putative process model	Example studies
				Motor	Interval	Motivation		
Go–NoGo	1 (but may vary)	1	No	++	n/a	++	Encode S – compare to C stored in LTM – decide whether to respond	Cook and Maunsell (2002), Stüttgen et al. (2006), Mehta et al. (2007), Palmer et al. (2007), Stüttgen and Schwarz (2008, 2010), Gerdjikov et al. (2010), O'Connor et al. (2010a,b), Frederick et al. (2011)
Yes/no	1	2	No	+	n/a	0	Encode S – compare to C stored in LTM – decide which response to emit	Britten et al. (1992, 1996), Krupa et al. (2001), de Lafuente and Romo (2005), Frederick et al. (2011), von Heimendahl et al. (2007)
Yes/no with reference	2	2	Depends on strategy	+	n/a	0	Encode R – transfer to WM – encode S – compare S&R – decide	Mountcastle et al. (1990), Purushothaman and Bradley (2005), Qin et al. (2009), also see Lee et al. (2007), Hautus et al. (2009)
Same-different	2	2	Depends on strategy	+	+	0	Encode S1 – transfer to WM – encode S2 – compare – decide	Vogels and Orban (1990)
m-Interval forced choice	m	m	Yes	+	+	0	For $m = 2$: encode S1 – transfer to WM – encode S2 – compare – decide	Hernandez et al. (1997), Luna et al. (2005)
Spatial *m*-alternative forced choice	m	m	No	+	n/a	0	For $m = 2$: encode S1 and S2 (simultaneously or sequentially?) – compare – decide	Mentzer (1966), Knutsen et al. (2006), Jacobs et al. (2009), Adibi and Arabzadeh (2011), Busse et al. (2011)

S, stimulus; S1, first stimulus; S2, second stimulus; RM, reminder; C, criterion; WM, working memory; LTM, long-term memory; ++, strong; +, moderate, 0, weak, n/a, not applicable.

observer is confronted with two different stimuli per trial; let us assume these are the same two stimuli that have been used previously in the YN task. The observer is presented with both stimuli on each trial, but each stimulus is assigned randomly to one of two successive temporal intervals. The observer's task is to designate which interval contained the target. Hence, contrary to the YN task, where the subject observes a sample from either the signal or the noise distribution on each trial, here the subject gets one sample from each without knowing which one is presented in which of the two intervals. The optimal strategy in this case is to take the difference between the two values and base the decision on the sign of the difference. **Figure 4** shows the two distributions that arise when the decision is based on the samples' difference. They represent the cases when (a) the first interval contained the target ($S \rightarrow N$) and (b) the second interval contained the target ($N \rightarrow S$). In the first case, the distribution of the differences will be centered on the mean of the *S* distribution minus the mean of the *N* distribution – thus, the mean difference will be d' as would be obtained in a yes/no task (henceforth referred to as d'_{YN}), with a variance of $\sqrt{2}$. In the second case, the distribution of the differences will be centered on the mean of *N* minus the mean of *S*, again with a variance of $\sqrt{2}$, but with a mean of $-d'_{\mathrm{YN}}$. Consequently, the distance of the two distributions is $2^* d'_{\mathrm{YN}}$. However, because of the increased variance,

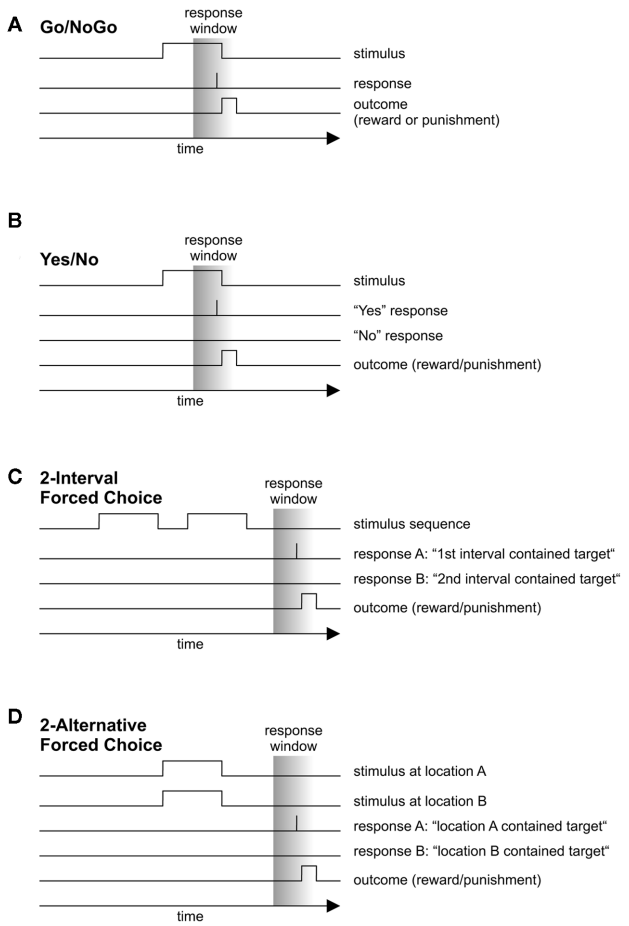

FIGURE 2 | Sequence of events in four tasks commonly employed in animal psychophysics. (A) Go–NoGo task. **(B)** Yes/no task. **(C)** Two-interval forced choice task. **(D)** Spatial two-alternative forced choice task.

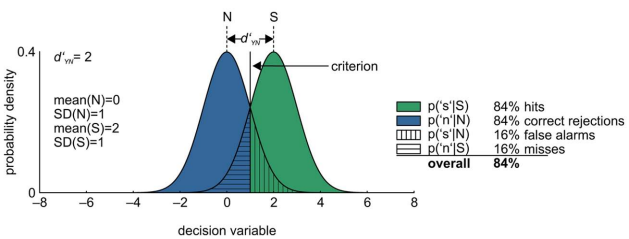

FIGURE 3 | Signal detection theoretical process model of performance in the yes/no task. See main text for details.

d' in the 2-IFC task (d'_{FC}) is $\frac{2^* d'_{YN}}{\sqrt{2}} = d'_{YN}{}^* \sqrt{2}$. Translated to correct performance, if chance performance equals 50%, this corresponds to an increase from 84% to 92% correct if $d'_{YN} = 1$. Thus, SDT predicts that an observer (if he adopts the optimal strategy) will have a $\sqrt{2}$ times higher discriminability (indexed by d'_{YN}) in a 2-IFC task than in a YN task with the very same two stimuli, i.e., $d'_{FC} = \sqrt{2}^* d'_{YN}$. Indeed, this prediction was approximately confirmed in some studies (Swets, 1959) but not in others (Yeshurun et al., 2008).

THE STIMULUS SET AND PRIOR PROBABILITIES

In most neurophysiological experiments, animals are presented with more than two stimuli varying in their discriminability. Each pair of stimuli has a specific d' that can be measured in an YN task as described above. Hence, each stimulus is assumed to give rise to a Gaussian distribution on the decision axis. How should the subject respond if we showed all stimuli randomized in one and the same block of an experiment? In **Figure 5A**, an observer is confronted with two stimulus categories, S1 and S2. S1 consists of a single stimulus (the noise-only stimulus N), S2 consists of five stimuli (each with a different d' compared to N). All six stimuli occur with equal probability (1/6) and the subject's task is to "detect" any stimulus that is greater than S1 in a simple YN task. The rightmost panel illustrates overall proportion of correct responses as a function of criterion placement. The resulting psychometric curve is depicted in **Figure 5E** (magenta), an example detection study which used such a stimulus set is Stüttgen et al. (2006).

Now consider a somewhat different situation: the stimuli are identical to those described above, but presentation of S1 is as likely as presentation of all stimuli in S2 taken together – thus $p(S1) = 0.5$, $p(S2) = 0.5$, and $p(S2_i) = 0.5/5 = 0.1$ for stimulus i, where i $\in\{1,2,3,4,5\}$. The optimal decision criterion has shifted considerably, and overall accuracy has dropped by 10% (see **Figure 5B**). The resulting psychometric function is shown in **Figure 5E** (blue), illustrating a marked reduction in the proportion of "S2" responses across all stimuli (for an example study, see Gerdjikov et al., 2010).

Imagine yet another situation: the observer is confronted with only two stimuli per session, S1 and one of the stimuli in category S2, in a series of YN experiments. This case is illustrated for two hardly distinguishable stimuli (**Figure 5C**) and two easily distinguishable stimuli (**Figure 5D**). For each of five possible pairs, percentage of correct responses can be calculated and used to construct a psychometric curve (**Figure 5E**, green). Of course, one could also conduct five consecutive 2-AFC or 2-IFC tasks, yielding somewhat higher performance (**Figure 5E**, red). As outlined in the previous section, 2-AFC/2-IFC performance (red) is consistently higher than YN performance (green) for ideal observers. This exercise illustrates an important point: psychophysical performance, measured in proportion correct responses, can be different under different tasks or even within the same task when identical stimuli occur with different probabilities. Notably, performance across tasks looks identical when transformed into the same unit of sensitivity, such as d'_{YN}.

THE MINIMALLY INFORMED OBSERVER

We can use the previous example to make another point. Regarding the NP comparison, it is crucial that the performance of the neurons is considered under the same constraints as the subject. In NP comparisons, the term "ideal observer" is often used very loosely to describe the optimal performance that an observer could achieve in the task given the neural recordings and some assumptions about the neural code. There is, however, also the question of how much of the task and the stimuli is known to the observer. In

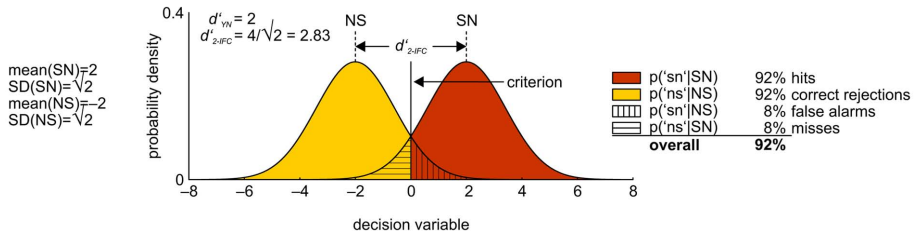

FIGURE 4 | Signal detection theoretical process model of performance in the 2-AFC task. See main text for details.

order to distinguish an observer that has all the information available that is also available to the experimenter (and might hence be called ideal) from the situation that the subject is in, Boneau and Cole (1967) coined the term "minimally informed observer" for a model that only uses the information that is available to the subject and nothing more.

Assume the subject is confronted with the situation depicted in **Figure 5B** – an YN task in which the S1 stimulus presentation probability is the same as that of all S2-stimuli together. In parallel, unit recordings from sensory neurons were obtained, and the experimenter wishes to relate the subject's performance to that of single neurons. The experimenter could, for example, compute ROC curves from the neuronal data for each pair of S1–S2 stimuli, and integrate the area under the ROC. The area under the ROC curve will correspond to the performance in a 2-AFC task if the difference model of SDT is correct and hence requires a correction of $\sqrt{2}$ to be comparable to an YN task. In **Figure 5E**, this amounts to a transition from the red to the green curve. Still, the neuron would be unfairly favored, since the analysis assumes a sequence of YN tasks with only two stimuli per block, while the observer was faced with six stimuli simultaneously. Contrary to the experimenter the observer does not know which stimulus is shown on each trial. Thus, the only possible strategy for the observer is to adopt a single decision criterion, as shown in **Figure 5B**. Optimal performance would accordingly result in the blue psychometric function in **Figure 5E**, and this is the correct analysis to apply to the neuronal data: to find a criterion which maximizes the percentage of correct responses when multiple stimuli can appear. Studies in which this procedure was applied include de Lafuente and Romo (2005) and Palmer et al. (2007).

PROCESS MODELS FOR PSYCHOPHYSICAL PERFORMANCE

Given the success of SDT in fitting psychophysical data, it is tempting to think of the calculations involved as actual cognitive processes. For the YN task, the sequence of steps can be conceptualized as follows: (1) encode the stimulus into the decision variable, (2) compare current value of the decision variable to the decision criterion retrieved from long-term memory, (3) decide on a response (**Figure 3**; see also Tanner, 1961). A process model for the GNG task with one stimulus per trial would be identical to that for YN, the difference being that, in YN, the observer has two response options (aside from non-task behavior), while in GNG, the observer has only one. Gomez et al. (2007) tested formal models of GNG and conclude that core processes of GNG and YN may be identical under some circumstances.

Two-interval forced choice is more complicated because there exist more than one process model for appropriate (but also suboptimal) behavior. (a) The observer could ignore the stimulus in the first interval altogether and treat this task as an YN task, basing his decisions only on sensory evidence gathered in the second interval; (b) he could do the converse and base his decisions only on the first interval. In these two cases, we would expect that he performs just the same way with two stimuli as in the yes/no task. Another strategy (c) that will give the same performance with regard to percent correct would be to perform two times YN in succession. If the stimulus is detected in neither interval, or if it is falsely detected in both, a random response is produced. Otherwise the interval in which a stimulus was detected is chosen. Yet, there is a fourth, the optimal strategy, (d) that was already discussed above (illustrated in **Figure 4**).

The important thing to note here is that, for a given psychophysical task, there may be more than one decision strategy to follow. It is often a convenient assumption that subjects follow the optimal strategy, but we must not forget that in most studies that conduct NP comparisons it is only an assumption. Consequently, both the processing required to yield a decision variable and the resulting performance may differ from subject to subject. Even if the sensory front end as an input to the system is fixed, subjects may use the available information in various, potentially suboptimal, ways. The 2-IFC task can however be adapted to force the animal to pay attention to both stimuli; see Romo and Salinas (2003).

A similar caveat as for 2-IFC applies to the use of the yes/no task with a reference stimulus (YNR, see **Box 1**), as for example used in Mountcastle et al. (1990); Purushothaman and Bradley (2005), Qin et al. (2009), and Bizley et al., 2010; also see Lee et al., 2007; Hautus et al., 2009). An analysis of the YNR task is depicted in **Figure 6**. Here, two stimuli per trial are presented. However, unlike 2-AFC/2-IFC, the first stimulus (reference, R) is identical for each trial, and the subject has to decide whether the second stimulus is more or less intense than R on some stimulus dimension. Again, the task is ambiguous as to its decision strategy. One strategy (the optimal one) is to ignore R completely and concentrate only on the second stimulus for decision-making. That way, YNR reduces to YN (**Figure 6A**). This assumes, of course, that all stimuli are known exactly to the subject. R is, however, only introduced because the experimenter thinks that this is not the case. One suboptimal strategy that seems likely is hence to (1) encode R, (2) encode the second stimulus, (3) take their difference, and (4) decide according to the sign of the difference; if

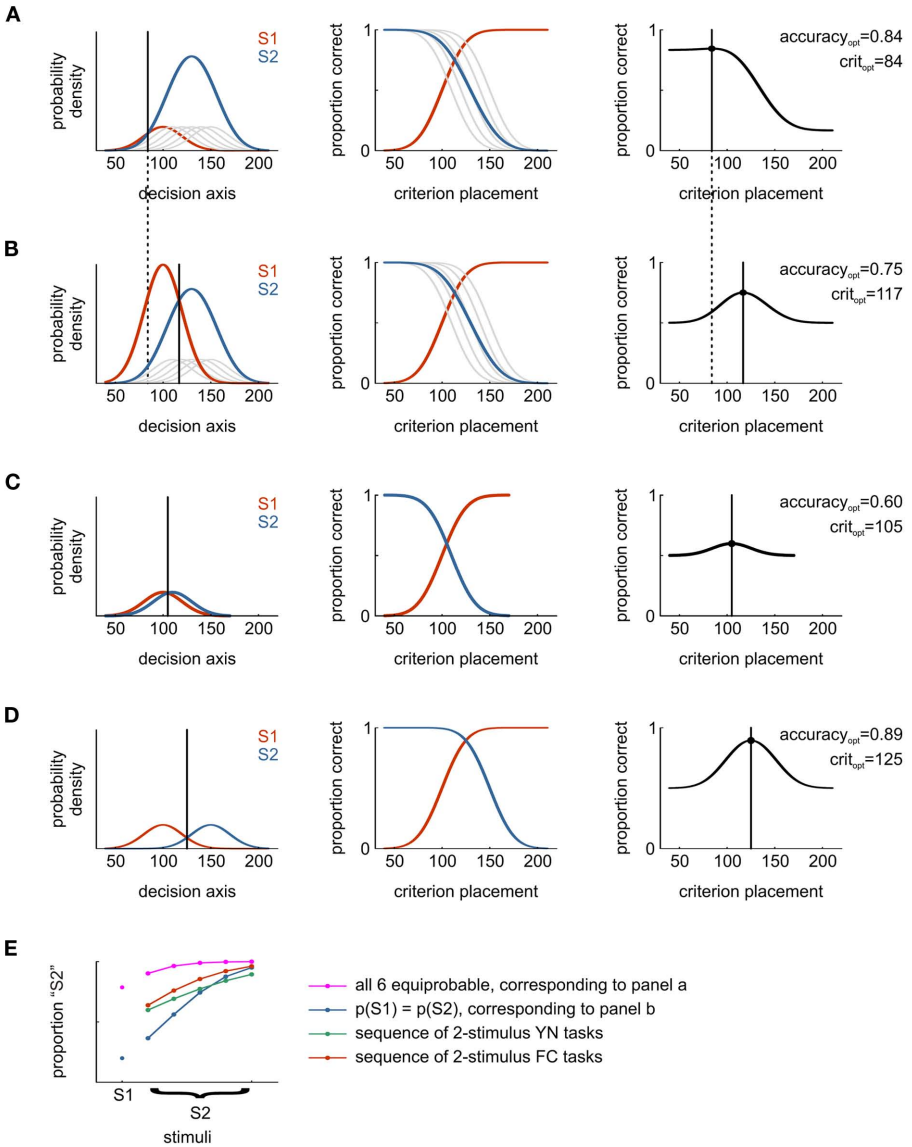

FIGURE 5 | Illustration how different stimulus presentation probabilities and different ROC-analysis strategies may yield disparate estimates of sensory performance. (A) The total stimulus set comprises six different stimuli, five of which correspond to S2 (gray distributions, blue distribution is the sum of five individual ones) and one corresponds to S1 (red). All six stimuli occur with equal probability (means: 100:10:150) and have identical SD (20). Middle panel: depending on the location of the response criterion on the decision axis, different sets of probabilities of a correct response exist. For each possible criterion on the abscissa, the corresponding accuracies for each stimulus can be read off the ordinate. Right panel: overall proportion of correct responses (across all stimuli) as a function of criterion placement. Vertical line indicates optimal criterion placement. **(B)** As in **(A)**, but probability of S1 and S2 are equal (0.5 each); within the S2 category, all stimuli are equally probable ($p = 0.1$). For the same set of stimuli as in a, the optimal criterion is shifted considerably to the right, and the overall proportion of correct responses drops from 0.84 to 0.75. **(C)** As in **(A)**, but showing performance in a two-stimulus yes/no task with S1 and one stimulus out of S2 with the weakest signal strength. **(D)** As in **(A)**, but showing performance in a two-stimulus yes/no task with S1 and one stimulus out of S2 with strongest signal strength. **(E)** Psychometric functions for different task conditions: magenta, task as in **(A)**, blue, task as in **(B)**, green: psychometric curve resulting from a sequence of separate yes/no experiments where stimuli are presented pairwise and in blocks (i.e., S2 vs. S1–S1, S2 vs. S1–S2, S2 vs. S1–S3 etc.), red: psychometric curve resulting from a sequence of 2-AFC experiments where stimuli are presented pairwise and in blocks.

positive, the second stimulus is deemed more intense (**Figure 6B**). This strategy is identical to the fourth strategy discussed in the context of the 2-IFC task; but this time, it yields suboptimal performance, decreasing 98% correct performance to 92% in the example. Furthermore, because of the ambiguity in task execution, it is unknown which neurometric analysis is most appropriate for this case.

One study actually demonstrated that, in YNR, animals ignore the reference stimulus and thereby follow the optimal strategy. Hernandez et al. (1997) trained monkeys to discriminate between

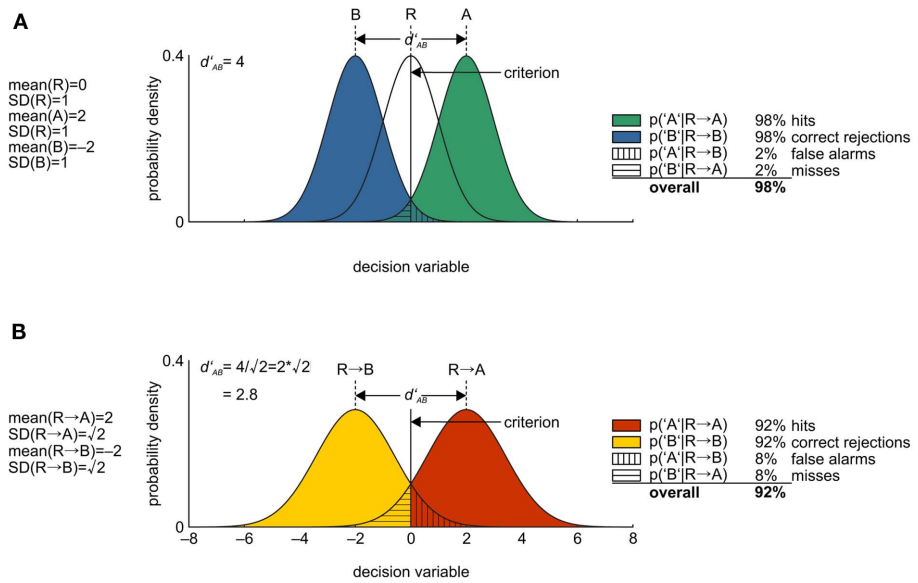

FIGURE 6 | Signal detection theoretical process models of performance in the yes/no task with reference stimulus. (A) Stimulus distributions along the decision variable under the optimal strategy. The reference stimulus sample is ignored on every trial, and thus the task reduces to the familiar yes/no task. **(B)** Stimulus distributions along the decision variable under the suboptimal strategy, when subjects decide on the basis of the difference of the first and the second sample.

two vibrotactile stimuli of different frequency. Monkeys were presented with a base stimulus first and a comparison stimulus second, and they had to judge whether the frequency of the comparison stimulus was higher than that of the base stimulus. Importantly, when the reference stimulus was omitted in control experiments, psychophysical performance did not change, suggesting that the reference stimulus has indeed been ignored by the animals. Also, when conditions were changed such that both base and comparison frequency varied randomly from trial to trial, performance dropped to chance levels, indicating that the animals did not perform the subtraction strategy as delineated above (**Figure 6B**).

While process models inspired by SDT make clear predictions for comparing performance across different psychophysical tasks, data supporting these models as description of an observer's decision strategy is sparse and conflicting. For example, Yeshurun et al. (2008) reexamined several claims about the 2-IFC method. They found, contrary to widespread belief, that the 2-IFC task is not unbiased: observers consistently prefer one of the two intervals, and this preference could not be explained by attentional state, complexity of the stimulus display, interstimulus interval (ISI), or experience of the observers. That 2-IFC is usually not unbiased was also remarked on by Klein (2001) and the topic was recently revisited by Garcia-Perez and Alcala-Quintana (2011) in a reanalysis of a large number of datasets. Moreover, sensitivity during the two intervals may differ: Yeshurun et al. (2008) provide some experimental evidence that d' in the first interval is larger than d' in the second interval. Similar observations have been reported and commented on by other authors (Nachmias, 2006; Ulrich and Vorberg, 2009; Ulrich, 2010). This asymmetry could be due to memory limitations, i.e., only a portion of the information from the first interval is retained, or due to perceptual interactions between the two presentation intervals. Importantly, Yeshurun et al. (2008) found no evidence that d' in 2-IFC is $d'_{YN} * \sqrt{2}$, as postulated by SDT. Thus, the standard SDT-difference model of 2-IFC performance was rejected, and the authors conclude that "we do not currently know how to model what observers actually do in 2-IFC tasks and that we have no reason to think that models appropriate to one choice of stimuli can be generalized to others." In a similar vein, Jäkel and Wichmann (2006) compared 2-IFC with spatial 2-AFC and spatial four-alternative forced-choice (4-AFC) in a contrast detection task and found that, surprisingly, 2-IFC with foveal stimulation produced the highest thresholds and 4-AFC with more peripheral stimulation the lowest thresholds in naïve observers, but not in a highly experienced one. In a discrimination task with similar stimuli, 4-AFC did produce higher thresholds than 2-IFC, as expected. Although their data do not allow a clear interpretation of how the psychometric functions from the different tasks relate to each other, the authors speculate that extra-sensory factors, like sensory memory and spatial attention, have different effects in different tasks. It is noteworthy that these extra-sensory effects are ignored in SDT.

On the neurometric side it makes sense to calculate sensitivity using the optimal procedure in order to get an upper bound on the performance that an ideal observer could achieve based on the neural data. We usually also assume that the whole observer behaves optimally when calculating psychometric sensitivity. We have to be aware, however, that the actual sensitivity of the observer may be higher than observed, since he may be using the information that is available to him in a suboptimal way. Ideally, obtained psychometric functions should index "true sensitivity" – i.e., measure discrimination performance of a sensory system and

be unaffected by choice of psychophysical method, variations in motivation, response measure, or response topography. The simultaneous measurement of neuronal and behavioral responses is considered the gold standard for conducting the NP comparison, because neuronal responses are not altered by anesthesia, the animal is actively engaged in the task, and stimulus variability across trials affects neurons and observer alike (Parker and Newsome, 1998). That way, important confounds inherent in comparing neurometric and psychometric data from different animals, such as plasticity of sensory representations during learning (Polley et al., 2004) or task-dependent changes in interneuronal correlations (Cohen and Newsome, 2008) are avoided. However, as outlined above, simultaneous acquisition of neurometric and psychometric data is not sufficient for conducting valid NP comparisons, because task-specific (and -unspecific, see below) factors may affect psychophysical performance without affecting neurometric performance. As a consequence, psychophysical performance will frequently fall short of true sensitivity.

ADDITIONAL FACTORS AFFECTING MEASURED DISCRIMINABILITY

Psychometric discrimination and detection performance for identical stimuli have been shown to be affected not only by type of task (see preceding section), but by a variety of other factors as well. SDT explicitly acknowledges the role of prior presentation probability and reinforcement history of the stimuli, but there exists a wide range of factors which, we believe, have been largely ignored in previous work. In the following paragraphs, we will review some non-sensory factors that are known to affect psychophysical performance. A short list of important factors in conducting NP comparisons is provided in **Table 2**.

Learning, motivation, and fatigue

One would expect psychometric functions to change based on learning and this is a good reason to work with highly trained observers and only analyze the responses after their performance does not improve anymore (Fine and Jacobs, 2002). This is of course the case for most animal experiments, especially those involving monkeys, even though some studies employing rats or mice sometimes stop training when an arbitrary performance criterion of, e.g., 80–85% has been achieved. Nevertheless, even within a session, a highly trained animal may show systematic deviations from stationarity. In order to achieve a high level of motivation, animals in psychophysical studies are usually food- or water deprived. Nienborg and Cumming (2009) used a yes/no task to assess disparity discrimination. They found that the delivery of larger rewards led to increased performance as measured by the slope of the psychometric function.

Hunger and satiety are known to offset response curves in psychophysical GNG tasks. Boneau and Cole (1967) separated response probabilities observed during the first half of an experimental session, when the subject was supposedly most hungry, from the second half of the session, when the animal was arguably less hungry; they observed a substantial decrease in overall response probability from the first to the second half of the session, which showed up at the level of the psychometric function as a shift of threshold. Similar effects are of course to be expected when the subject gets tired. In order to detect such non-stationarities, one possibility is to compute a rank-biserial correlation between trial number and responses (e.g., 1 for correct and 0 for incorrect; see Stüttgen and Schwarz, 2008). Ideally, the correlation should be 0. If the correlation assumes negative values, the number of correct responses is increasing over the duration of the session. As another means to detect such effects, Wichmann and Hill (2001a,b) describe a statistical test that uses the order of the blocks in a constant stimuli design to predict the residuals for the fit of the psychometric function. Fruend et al. (2011) assess the severity of such violations on the estimation of psychometric functions and suggest a suitable correction for the resulting confidence intervals.

Table 2 | Overview over the most frequent factors potentially affecting the NP comparison.

Temporal uncertainty (stimulus onset and offset not made explicit in detection task)
Stimulus uncertainty (presenting more than two stimuli per block of trials, or presenting novel stimuli)
Stimuli for neurometric and psychometric data collection differ appreciably
Neurometric data gathered with different animals, under anesthesia or *in vitro*
Ambiguous task structure (e.g., yes/no with reminder)
Subject not trained to asymptotic performance
Subject lacks motivation
Subject is inattentive
Response bias

Attention

Animals are presumably inattentive to the task a significant portion of the time. In principle, this problem is unrelated to the psychophysical task employed, but it may be especially detrimental in GNG. Lapses of attention in GNG will tend to yield fewer responses overall and thereby increase the measured threshold. In GNG, the experimenter has no way to identify whether the absence of a response in a given trial is indeed based on assessment of the sensory evidence in a trial or due to non-sensory factors such as lapse of attention or decreased motivation. However, even in YN and FC, this may cause problems if the animal does not simply refrain from responding on such trials, but instead presses buttons or makes saccades at random. To complicate issues further, it could be that, beyond non-sensory influences on response bias, sensitivity itself could be affected by fluctuations of attention. For example, Treue and Martinez Trujillo (1999) reported that tuning curves of neurons in MT are gain-controlled by attention. Assuming spike count as the relevant code, this could affect performance if neurons tuned to the stimulus increased their firing rate while the firing rate of "comparison neurons" not tuned for the stimulus, remained the same; in SDT terms, the mean of the signal distribution would move away from the mean of the noise distribution, yielding an increase in d'. To control for fluctuations in attention within a session, experimenters can follow strategies as suggested in the previous section on motivation and fatigue.

Working memory

In GNG and YN tasks, working memory is not required in the sense that sensory information needs to be maintained over a short time span, e.g., a visual or auditory signal (this is not meant to imply that task execution is completely independent of working memory, as the animal needs to recall what task to perform, which lever or button to press under what circumstances etc.). In 2-IFC, SDT assumes perfect retention of the first stimulus, regardless of the ISI. If the sequence of the stimuli is seamless, no working memory is needed and discriminability depends on the temporal contrast of the two stimuli. In this case, the 2-IFC paradigm tests predominantly sensory coding. If, however, the stimuli are separated by a non-zero ISI, storing and retrieving stimulus properties in working memory plays a decisive role. Importantly, performance in 2-IFC is affected by the duration of the ISI. If the ISI is too long, performance decreases (Harris et al., 2001). It is a welcome recent development in neurophysiology that the mechanisms of sensory working memory are under investigation (Romo et al., 1999). The interplay between simple psychophysical paradigms and working memory is certainly a worthwhile field of theoretical and experimental development (Machens et al., 2005). In any case, it is likely that neurometrics in 2-IFC overestimate performance when sensory neuron responses during the first stimulus period are used, rather than the memory trace of the first stimulus as represented by working memory neurons.

Sequential effects

Boneau et al. (1965) showed that, at the level of individual trials, non-rewarded stimuli are more likely to elicit a response when they immediately follow a rewarded trial (in a GNG task). In addition, Busse et al. (2011) report that animals tend to switch sides after each trial, regardless of success or failure. Verplanck et al. (1952) have shown that for human subjects trials in a detection experiment are not independent – contrary to the usual assumption, subsequent trials in a detection experiment were positively correlated. If these effects were just due to higher cognitive effects, like the gambler's fallacy, then perhaps there would be hope that their effects could be minimized by instruction or training. However, there are indications that the sequential effects are a trace of the mechanisms that produce the observed behavior. For identification tasks (such as the YN task) it seems likely that the subject needs to store the ideal stimuli in long-term memory and then compares the stimulus on each trial to the stored representations to decide on a response. However, Stewart et al. (2005) argue that in many cases long-term memory is not necessary and that a simple mechanism that only compares the current stimulus to the last trial can explain many aspects of the data. For detection tasks, Treisman and Williams (1984) have argued that the sequential effects arise through an adaptive setting of the criterion based on previous trials. If this was the case then the fluctuations in the criterion should be taken into account when assessing a subject's sensitivity, e.g., by separating trials according to stimuli presented in each preceding trial.

Stimulus set

The measured psychophysical discriminability of two given stimuli can depend on whether, which and how many other stimuli constitute a stimulus set in an experimental session (Stüttgen, unpublished data).

In many psychological experiments the stimulus range can influence the behavior that one wants to measure, often with unexpected results (Poulton, 1975). For example, Lages and Treisman (1998) show that a task that suggests comparison of a stimulus to a reference stimulus from long-term memory is actually solved by the subject by taking into account the stimulus range without recourse to the reference stimulus at all (a possible explanation for this can be found in Treisman and Williams, 1984).

A related problem is that, in many neurophysiological studies, details of the stimuli (e.g., retinal position, motion direction, contrast etc.) are meticulously matched to the receptive field properties of the neuron currently under study, in order to maximize the chance that this neuron is actually involved in the psychophysical task. However, because this stimulus adaptation has to be done for each single unit recording (see Britten et al., 1992), it may have detrimental effects on the performance of the subject which is required to generalize the task across a large variety of stimuli, many of which it may never have seen before. For most sensory areas, it is commonly assumed that the neural response to a stimulus is thought to be largely unaffected by stimulus history, as long as some reasonable ISI is provided. Accordingly, neural representation of a given stimulus should remain unaltered by the number of stimuli in a stimulus set, while psychophysical performance is not. Therefore, experimenters should take care to meet the assumptions of SDT lest the subjects exhibit suboptimal performance.

Temporal and stimulus uncertainty

It is often neglected that ideal observer analysis of spike responses using SDT (construction of ROC curves) requires some assumptions that are frequently not met by experimental conditions. SDT analysis assumes that the observer knows everything about the signal, including starting time, duration, phase, frequency, amplitude, and location – a prerequisite sometimes referred to as "signal specified exactly." If experimental subjects are uncertain as to any of these parameters, performance decreases (Shipley, 1960; Swets et al., 1961; Green and Weber, 1980; Green and Forrest, 1989).

Many neuroscience studies aiming at the NP comparison violate at least one of these assumptions; most often, multiple stimuli are used per experimental block (see stimulus range), or the timing of the stimulus is held uncertain (e.g., de Lafuente and Romo, 2005; Stüttgen et al., 2006). Hernandez et al. (1997) compared monkeys' performance for vibrotactile frequency discrimination in two different tasks: yes/no with reference stimulus and 2-IFC with variable stimulus pairs across trials. The monkey's difference limina in the first set of experiments were lower by ∼30% (thus, sensitivity was higher). This effect is likely due to the added stimulus uncertainty, because performance in the second experiment would be expected to *increase* according to SDT. Assuming that neural responses were not systematically affected by task type, the NP comparisons would yield different results for the two sets of experiments.

WHICH TASK IS BEST SUITED FOR THE NEUROMETRIC–PSYCHOMETRIC COMPARISON?

Blackwell (1952) systematically compared psychophysical methods for measuring visual thresholds in human subjects. He concluded that the 2-IFC method is superior to YN on several indices of quality, including reliability of threshold measurement (variability of repeated assessments of threshold), vulnerability of threshold measurement to non-sensory biasing factors (i.e., procedural factors such as background illumination, number, spacing, and order of stimuli, whether feedback was provided, and whether financial incentives for optimal performance was offered), and the absolute magnitude of the psychophysical threshold. Jäkel and Wichmann (2006) reinvestigated this issue and confirmed Blackwell's earlier results for a visual detection task – however, only for experienced observers. For naïve observers, in contrast, spatial 4-AFC was superior in terms of reliability, bias, sensory determinacy, and efficiency of measurement. For animal subjects, Mentzer (1966) has conducted similar comparisons of YN, 2-AFC, and 4-AFC for light detection in pigeons, but could not find any performance differences. Frederick et al. (2011) conducted a comparison of GNG and YN for odor discrimination and also found no evidence for major differences in resulting performance.

Most psychophysical studies employing unit recordings in primates have used the YN method, even though it is usually referred to by another name (e.g., Britten et al., 1992, 1996; Dodd et al., 2001; Uka and DeAngelis, 2003; Heuer and Britten, 2004; de Lafuente and Romo, 2005; Nienborg and Cumming, 2006, 2007, 2009); some have used GNG (Cook and Maunsell, 2002; Palmer et al., 2007); or some other method (YNR: Mountcastle et al., 1990; Purushothaman and Bradley, 2005; Qin et al., 2009; Bizley et al., 2010; same-different: Vogels and Orban, 1990). A series of studies by the Romo group has consistently employed 2-IFC (Romo et al., 1999; Hernandez et al., 2000; for review, see Romo and Salinas, 2003). To our knowledge, psychophysics with concomitant unit recordings in other species – most notably rats and mice – have so far almost exclusively relied on GNG (Stüttgen et al., 2006; Mehta et al., 2007; Stüttgen and Schwarz, 2008, 2010; Andermann et al., 2010; Gerdjikov et al., 2010; O'Connor et al., 2010a,b) or YN (Krupa et al., 2001; Prigg et al., 2002; Feierstein et al., 2006; von Heimendahl et al., 2007; Kepecs et al., 2008; Frederick et al., 2011). However, these species can be trained on FC tasks as well (pigeons: spatial 2-AFC: Blough, 1971; 4-AFC: Mentzer, 1966; mice: 2-AFC, Jacobs et al., 2009; Busse et al., 2011; Haiss et al., submitted; rats: 2-AFC: Knutsen et al., 2006; Adibi and Arabzadeh, 2011). We know of no study with these species which employed the *m*-IFC task; still, since rats, mice, and pigeons are known to learn delayed matching-to-sample problems (rats: Kesner et al., 1996; mice: Goto et al., 2010; pigeons: Lissek and Güntürkün, 2004), it should be possible to train them on *m*-IFC as well. To sum up, while most studies have so far employed YN, other methods seem feasible. It is common understanding in the community of researchers (based on anecdotal evidence) that GNG is trained faster than YN (but see Frederick et al., 2011), which again may be trained faster than IFC. More effort is required to make all psychophysical tasks routinely available for future psychophysical research. Spatial *m*-AFC has the disadvantage that, since several stimuli are presented simultaneously, it is difficult to control for repetitive shifts of attention during the course of a single trial, and to attribute modulations in unit activity to any one stimulus, as opposed to the entire stimulus display. *m*-IFC avoids this problem because stimuli are presented successively. On the other hand, *m*-IFC requires working memory for the stimulus during the ISI (unless the interval is zero). In addition, all FC variants (as well as YNR) leave room for different decision strategies (see above), which need to be properly assessed before conducting the NP comparison. GNG and YN methods have the advantage that no sequential or simultaneous stimulus presentation is required. Accordingly, no working memory for a sensory stimulus is necessary, which potentially simplifies the task. We believe that the YN method is particularly well suited for NP comparisons. Unlike GNG, lapses of attention, or impulsive responding do not directly contaminate the response measure, compared to FC and YNR, there are less degrees of freedom in terms of strategy to employ, although we regret to say that there are no good data to back up this claim, and these data are badly needed.

CONCLUSION

The comparison of neurometric and psychometric sensitivity is fraught with problems. We have argued in this review that, in stark contrast to estimation of neurometric sensitivity, problems with the estimation of psychometric sensitivity have been largely ignored in the literature on the physiology of perception. Nevertheless, on both sides significant progress will be needed to make NP measurements more precise. Here we list some recommendations for future work originating from the points raised in this review.

On the neurometric side, we see the research program based on recording single neurons while activating them with sensory stimuli coming to an end. This approach has been invaluable to demonstrate that the neurometric sensitivity of single cells most often reaches close to (but hardly surpasses) that of the observer, thus fostering a central tenet of theories of sparse coding, as predicted by Barlow and Mountcastle. However, beyond showing sparse coding to be feasible in principle, this approach helps little in elucidating the role of the large neural populations activated even by near-threshold stimulation. The goal of today must be to characterize the neuronal code of the population of neurons carrying precisely the information leading to behavior. The need to define and access informational bottlenecks renders this a tough task. Retinal ganglion cells have been spotted to be one such bottleneck and should be exploited further. The creation of bottlenecks by juxtacellular stimulation and soon by optogenetic means will allow carrying this research program further both in rodents and in monkeys. In passing, we point out that bottlenecks can be found and/or created very easily in invertebrate model systems which sometimes employ just single or a few neurons to carry lifesaving, and thus, evolutionary relevant information. An instructive example has been provided by Roeder in his studies of noctuid moths. These insects use auditory information from just two neurons per ear to decide on different tactics to escape foraging bats (Roeder, 1966). Insects exhibit complex types of behavior, such as working memory and decision making (Menzel and Giurfa, 2001; Pompilio et al., 2006). Also, they offer exquisite experimental flexibility in terms of genetic manipulation

and optical imaging of neuronal function (Briggman et al., 2005; Haehnel et al., 2009). Accordingly, invertebrates may serve as valuable model systems to investigate the physiology of perception, and to offer useful insights for the studies of mechanisms of perceptual decision making in mammals.

On the psychometric side, the importance of task structure and other non-sensory factors relevant for psychophysical performance must be acknowledged. More effort is needed to validate the measurements of psychometric sensitivity by deliberate variation of task structure while maintaining a constant stimulus set. For instance, results from YNR or FC studies that allow ambiguous interpretations in terms of underlying cognitive processes can be validated by applying YN tasks. Formal models of the cognitive processes underlying different tasks need to be refined and pitted against each other both with purely behavioral tests (Gomez et al., 2007; Jang et al., 2009; Wolfe and Van Wert, 2010; Frederick et al., 2011; Stüttgen et al., 2011) and with neural recordings (Smith and Ratcliff, 2004; Gold and Shadlen, 2007; Churchland et al., 2008; Kepecs et al., 2008). It is unclear what kind of comparison process underlies perceptual decisions, i.e., what is actually compared (Stüttgen et al., 2011). The effect of storing sample stimuli and/or decision criteria in long-term and working memory against which current sensory information can be compared demands clarification. As shown in **Figure 5**, psychometric performance for identical stimulus discriminations can be wildly different dependent on presentation strategy. Thus, psychometric performance must be compared with presenting pairs of stimuli vs. a whole stimulus array, and algorithms to calculate optimal neurometric sensitivity must be adjusted to reflect the animals' optimal strategy, given these circumstances. For further studies of neural coding in sensory system, we hold it vital to acknowledge that clean estimates of "true" psychophysical sensitivity cannot be obtained without appropriate models of perceptual decision-making. Such models need not only isolate sensitivity from response bias (Tanner and Swets, 1954; McCarthy and Davison, 1981; Busse et al., 2011) but from other factors affecting observed performance as well, be they inherent to the psychophysical task or not.

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Challenges of interpreting frontal neurons during value-based decision-making

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The frontal cortex is crucial to sound decision-making, and the activity of frontal neurons correlates with many aspects of a choice, including the reward value of options and outcomes. However, rewards are of high motivational significance and have widespread effects on neural activity. As such, many neural signals not directly involved in the decision process can correlate with reward value. With correlative techniques such as electrophysiological recording or functional neuroimaging, it can be challenging to distinguish neural signals underlying value-based decision-making from other perceptual, cognitive, and motor processes. In the first part of the paper, we examine how different value-related computations can potentially be confused. In particular, error-related signals in the anterior cingulate cortex, generated when one discovers the consequences of an action, might actually represent violations of outcome expectation, rather than errors *per se*. Also, signals generated at the time of choice are typically interpreted as reflecting predictions regarding the outcomes associated with the different choice alternatives. However, these signals could instead reflect comparisons between the presented choice options and previously presented choice alternatives. In the second part of the paper, we examine how value signals have been successfully dissociated from saliency-related signals, such as attention, arousal, and motor preparation in studies employing outcomes with both positive and negative valence. We hope that highlighting these issues will prove useful for future studies aimed at disambiguating the contribution of different neuronal populations to choice behavior.

Keywords: value, reward, choice, decision-making, prediction error, valence, orbitofrontal, anterior cingulate

INTRODUCTION

Some of the first recordings of single neuron activity in frontal cortex noted the presence of neurons with various reward-related responses. Recordings in orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC) found neurons that were active to cues that predicted reward, neurons that fired immediately preceding and during an expected reward and neurons that responded to the omission of an expected reward (Niki and Watanabe, 1976; Rosenkilde et al., 1981; Thorpe et al., 1983). Similar neurons were subsequently found throughout the frontal cortex (Ono et al., 1984; Watanabe, 1996; Leon and Shadlen, 1999; Amador et al., 2000; Roesch and Olson, 2003) and indeed in parietal (Platt and Glimcher, 1999), temporal (Liu and Richmond, 2000), and occipital cortex (Shuler and Bear, 2006). Due to the central role that reward plays in behavioral control, many cognitive processes can correlate with reward, so it is critical to define precisely the aspect of reward processing in which specific neuronal populations are engaged. Our review will focus on OFC and ACC. Even though reward-related responses are found throughout the frontal lobe, it is only damage to these two areas that produces a specific deficit in value-based decision-making (Bechara et al., 1998; Kennerley et al., 2006; Fellows and Farah, 2007).

Current theoretical models of value-based decision-making posit a series of distinct stages (Padoa-Schioppa, 2007; Rangel and Hare, 2010). First, the subject calculates the value of possible behavioral outcomes to derive a "goods space." This involves integrating the multiple parameters that go into making one outcome more preferable than another such as subjective preferences, magnitude of reward, or delay until reward delivery. Second, the subject calculates action values by subtracting the action costs involved in acquiring the goods from the value of the goods themselves. The separation of goods and actions makes sense from a computational perspective. The parameter space of potential goods and the space of possible actions are both vast and the complexity can be reduced by calculating the value of goods and actions independently. In addition to an argument from parsimony, neuroimaging findings support the notion that subjects can make choices in a goods space that is independent of action (Wunderlich et al., 2010), and these goods-based calculations appear to occur in OFC.

Within this framework it is evident that spurious correlations with goods values or action values might occur either upstream or downstream of the decision-making process. Calculating the value of a good requires the integration of its costs and benefits. For example, humans often calculate a good's value by integrating its desirability and price. The Porsche looks great; the price tag not so much. Similarly, animals often have to weigh the desirability of a good with relative availability in the environment (Stephens and Krebs, 1986). Performing these calculations

requires the integration of multiple sensory parameters that must be represented upstream of the calculation. Problematically for the interpretation of value signals, these sensory representations can easily correlate with the good's value. For example, a large piece of fruit is more rewarding to a hungry animal than a small piece of fruit. Thus, the firing rate of visual sensory neurons would correlate with the fruit's value, even though they are simply responding to the visual representation of the fruit's size rather than its value *per se*. Although our focus is on the frontal cortex, there is a good deal of sensory information encoded in this part of the brain that is relevant to the representation of rewards. For example, the ventral surface of the frontal lobe includes primary gustatory cortex and primary olfactory cortex (Cavada et al., 2000).

In order to dissociate value responses from the sensory responses that go into the value computation, it is important to show that the neuron responds to multiple dimensions of the value space. For example, if the same neuron increases its firing rate as the desirability of a good increases and decreases its firing rate as the price of that good increases, then we can reasonably conclude that the neuron encodes net value as a combination of costs and benefits. Neurons encoding multidimensional aspects of value have been identified throughout frontal cortex. For instance, we trained animals to perform a multidimensional choice task (**Figures 1A–C**) in which they had to make choices based on the magnitude of a juice, its probability of delivery and amount of work necessary to earn the juice (Kennerley et al., 2009). We found neurons encoding every decision variable and every combination of decision variables in ACC, OFC, and lateral prefrontal cortex (**Figure 1D**). Other groups have found prefrontal neurons that integrate the magnitude of a juice with its probability of delivery (Amiez et al., 2006), subjective preference for the juice (Padoa-Schioppa and Assad, 2006) and delay until its delivery (Hwang et al., 2009). Thus, there is ample evidence that frontal neurons do not solely respond to sensory dimensions of a good, but instead integrate multiple attributes that, in sum, determine the value of the good.

Downstream of the decision-making process, things are more complicated. Value signals can serve many different functions, including the reinforcement of behavior, the evaluation of alternative courses of action, and the prioritization of limited capacity behavioral and cognitive resources (Wallis and Kennerley, 2010). This means that neurons encoding other processes such as arousal or attention could correlate with expected value even though they are not encoding the value *per se* (Maunsell, 2004; Luk and Wallis, 2009). In the rest of this paper, we examine several places where these processes confuse the interpretation of value signals, and discuss attempts to disentangle them from the decision-making process.

PREDICTIONS, ERRORS, AND PREDICTION ERRORS

Value signals continue to be important even once a decision has been made and an action completed. Notably, the outcome of one's choices can be used to guide future decisions, thereby ensuring adaptive and efficient behavior. If the outcome of a choice was more valuable than expected then you should be more inclined to choose in a similar manner in future. In contrast, if the outcome was less valuable than expected, you should be less inclined to make that choice again. The difference between the value of the expected outcome and the actual outcome is termed the prediction error, and was famously identified to be encoded by dopamine neurons in the ventral midbrain (Schultz et al., 1997). In this section, we examine to what extent value coding in frontal cortex relates to value predictions and prediction errors.

NEUROPHYSIOLOGICAL PROPERTIES OF ACC

Early single-unit recordings in ACC observed strong firing when a monkey made an error (Niki and Watanabe, 1979). Human neurophysiology studies later reported a negative potential over ACC when subjects made errors (Gehring et al., 1990; Falkenstein et al., 1991; Ito et al., 2003), which became known as the error-related negativity (ERN). Error signals were also observed using fMRI (Carter et al., 1998; Ullsperger and Von Cramon, 2003; Holroyd et al., 2004), and theories emerged suggesting that ACC was important for processing negative events, costs, or errors (Aston-Jones and Cohen, 2005) or monitoring for conflicts between competing types of information (Botvinick et al., 2004; Ridderinkhof et al., 2004). However, the picture emerging from single-unit studies soon became more complex.

In a task requiring a monkey to learn action–outcome associations using secondary reinforcers, ACC neurons were just as likely to respond to positive feedback as negative feedback and, furthermore, the response to positive feedback was strongest early in learning (Matsumoto et al., 2007). Thus, the neurons' response was strongest when the feedback was least expected, and weakest when it was fully predicted, exactly what one would expect from a prediction-error signal. ACC neuronal activity has also been recorded during the performance of a competitive game (Seo and Lee, 2007). On each trial, monkeys and a computer opponent chose one of two identical targets. Reward was delivered if both subject and computer chose the same target. Choice strategies were exploited by the computer opponent, so optimal behavior entailed choosing randomly. However, the monkeys did not behave completely randomly and their behavior indicated that they were estimating the long-term value of the response options. Many ACC neurons responded during the feedback period in a way that reflected both the value of the feedback (whether or not the animal received a reward) and the animal's estimation of the choice's long-term value, consistent with a reward prediction error.

However, subsequent studies revealed a more complex picture. For example, ACC neurons were recorded while an animal searched among four targets using trial and error to find the one associated with reward (Quilodran et al., 2008). Sometimes the animal would get lucky and discover the reward with the first target it selected. Sometimes it would not discover the rewarded target until the other three had been ruled out. Once the animal discovered the rewarded target, it was allowed to select it several more times and earn several more rewards. Similar to previous studies, many neurons responded to reinforcement. Responses were strongest when the correct target was first discovered and weaker when the target was reselected in order to receive more reward. However, the authors noted that the response did not resemble a prediction error. The response to the correct target was the same irrespective of whether it was selected on the first try (i.e., when there was a one in four chance of being correct) or whether it was

only selected after the other three targets had been ruled out (in which case the reward was certain). In other words, in this task the animal's prior expectancy of receiving a reward did not affect the neuronal response.

In order to clarify the role of ACC neurons in encoding reward prediction errors, we analyzed data from a task that minimized the effects of learning by using overlearned stimuli (**Figure 1**). The monkey had learned the probability with which these stimuli predicted reward delivery over many thousands of trials such that their presentation would produce a specific expectancy of reward. A similar approach helped to delimit prediction errors in dopamine neurons (Fiorillo et al., 2003). We found a broad variety of responses in ACC neurons (**Figure 2**), including neurons that encoded whether something was better than expected (**Figure 2A**, positive prediction error) or worse than expected (**Figure 2B**, negative prediction error; Kennerley and Wallis, in press). Other groups, adopting a similar approach, have found that ACC neurons encode a saliency signal (i.e., whether an outcome

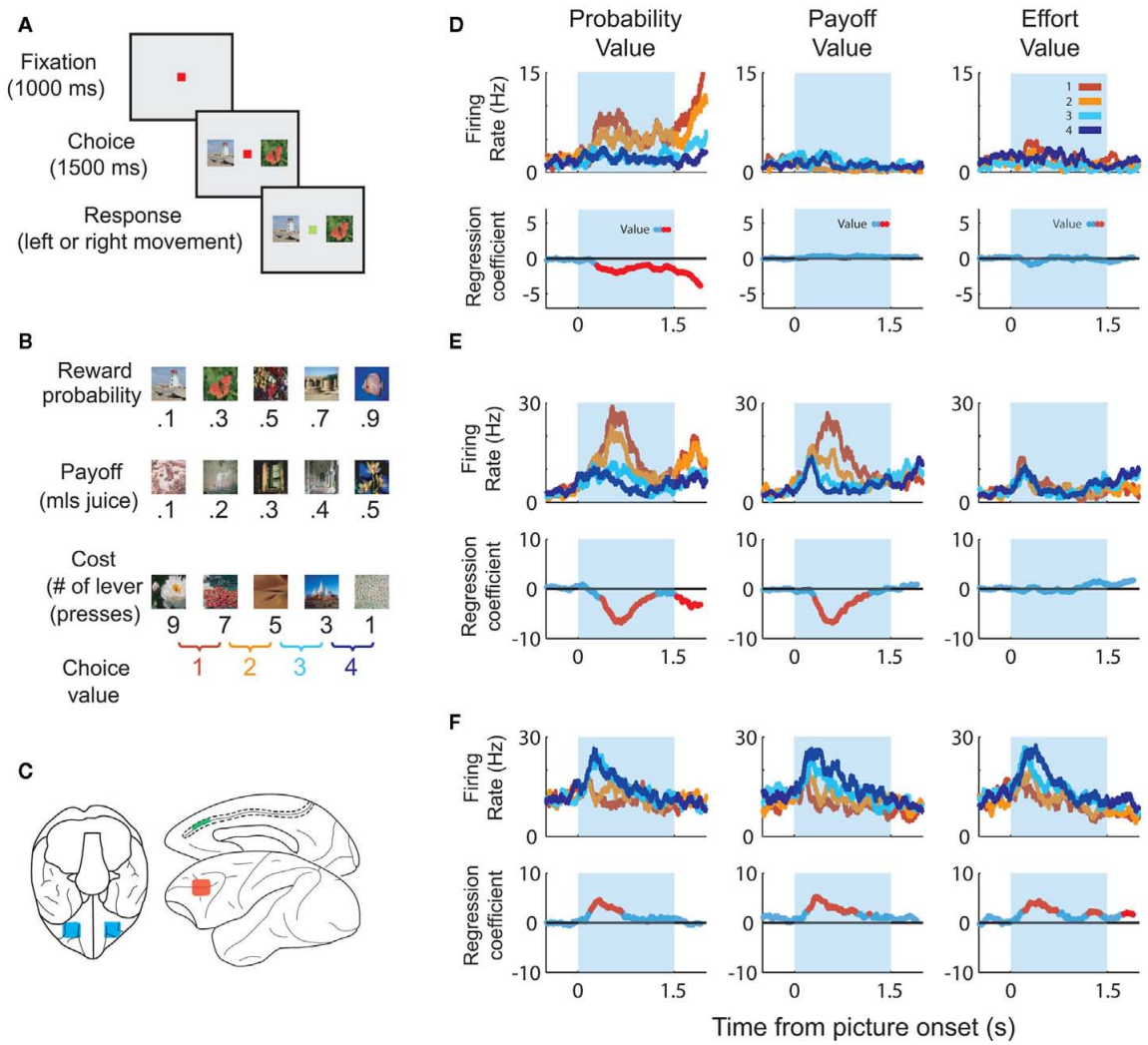

FIGURE 1 | Task parameters associated with the multidimensional choice task. (A) The task began with the subject fixating a central spot. Two pictures appeared, one on the left and one on the right. When the fixation spot changed color the subject selected one of the pictures and received the associated outcome. **(B)** Each picture was associated with a specific outcome. The "probability" pictures were associated with a set amount of juice, delivered on only a certain fraction of the trials. The "payoff" pictures were associated with different amounts of juice reward. The "cost" pictures were associated with a specific amount of juice, but the subject had to earn the juice by pressing a lever a different number of times. We only presented pairs of pictures that were from the same set and that were adjacent to one another in terms of value. Thus, for each set of pictures there were four potential choices. **(C)** The approximate locations that we recorded in OFC (blue), ACC (green) and lateral prefrontal cortex (red). **(D)** The upper row of plots illustrates spike density histograms from a single ACC neuron sorted according to the value of the expected outcome of the choice. The lower row of plots illustrates a statistical measure of the extent to which the variance in the neuron's firing rate can be explained by the value of the choice. Portions of the curve shown in red indicate significant encoding of value at those time points. The neuron encodes value solely on probability trials with an increase in firing rate as the value of the choice decreases. **(E)** An ACC neuron that encodes value on probability and payoff trials, increasing its firing rate as value decreases. **(F)** An ACC neuron that encodes value for all decision variables, increasing its firing rate as value increases.

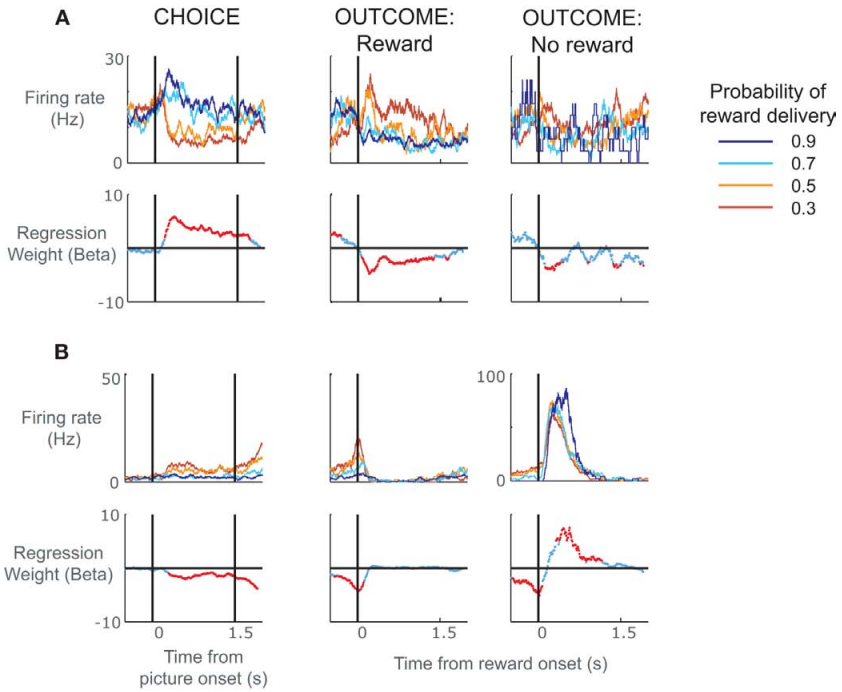

FIGURE 2 | Spike density histograms illustrating single neurons that encoded value information during the choice as well as the subsequent outcome of the choice. (A) The top row of plots consists of spike density histograms recorded from a single ACC neuron and sorted according to probability of reward delivery as indicated by the pictures. The three plots show activity during the choice phase, the outcome phase when a reward was delivered, and the outcome phase when a reward was not delivered. For the choice phase, the vertical lines relate to the onset of the pictures and the time at which the subject was allowed to make his choice. For the outcome phase, the vertical line indicates the onset of the juice reward. The lower row of plots indicates neuronal selectivity determined using regression to calculate the amount of variance in the neuron's firing rate at each time point that can be explained by the probability of reward delivery. Red data points indicate time points where the probability of reward delivery significantly predicted the neuron's firing rate. The neuron responded during the choice phase when pictures appeared that predicted reward delivery with high probability. It also responded during reward delivery, but only when the subject was least expecting to receive the reward. It shows little response when the subject did not receive a reward. In other words, the neuron encoded a positive prediction error, i.e., it responded when either choice offerings or outcomes were better than expected. **(B)** An ACC neuron that encoded a negative prediction error, i.e., it responded when events occurred that were worse than expected. The neuron responded when pictures appeared that predicted reward delivery with low probability, showed little response to the delivery of reward, and responded when reward was not delivered, particularly when the subject was expecting to receive a reward.

was unexpected irrespective of whether it was better or worse than expected; Hayden et al., 2011) as well as "fictive" error signals, neuronal responses to outcomes for actions that one did not take (Hayden et al., 2009).

Thus, the picture that is emerging from ACC is of an area that encodes a variety of signals that would be useful for learning, with a common thread being that they integrate information about the outcome of actions and their relationship to prior expectancies. This contrasts with activity recorded from dopamine neurons, where the vast majority of signals correlate with reward prediction errors (Fiorillo et al., 2003; Bayer and Glimcher, 2005; Bayer et al., 2007), encoding positive prediction errors with increased firing rates and negative prediction errors with decreased firing rates. ACC neurons also encode prediction errors, but with a good deal more heterogeneity. This heterogeneity should not be surprising. Cortex is responsible for performing multiple computations in parallel and integrating a diversity of information. Even neurons in primary sensory areas encode multiple parameters of a stimulus space (Carandini et al., 2005). In contrast, signals from neurotransmitter systems appear more uniform, performing a single computation and broadcasting it to a large portion of the brain (Schultz, 1998; Yu and Dayan, 2005), although we note that recent studies have challenged whether signals from neurotransmitter systems are quite as homogenous as originally thought (Bromberg-Martin et al., 2010).

In our study, we found that the activity of ACC neurons during the feedback period tended to match that in the choice period. If a neuron responded to rewards that were better than expected, it also tended to respond when the choice was between better than average alternatives. For example the neuron shown in **Figure 2A** had the largest responses during the outcome period when the picture associated with a low probability of receiving reward unexpectedly resulted in reward, that is, it responded when the outcome was better than expected. During the choice period, the very same neuron had highest firing rates when the monkey was presented with the option to choose a picture with high reward probabilities, and lower firing rates when his best option was a lower probability picture. Because we always presented pictures that were adjacent in value (**Figure 1B**) and the subjects virtually always chose the best option, we cannot determine whether this activity is related to the

average value of the two stimuli or the higher-valued chosen stimulus. In either circumstance, however, the neuron could be viewed as responding to a situation that is better than expected, which, during the choice phase, was the presentation of stimuli indicating the highest probability of receiving a reward. This raises the question of whether we should reinterpret our original conclusions regarding ACC activity during the choice phase as encoding differences between the value of the present options and the average choice value (i.e., a choice prediction error) rather than the value of the choice *per se*.

Studying decision-making requires presenting subjects with choices. This is typically done in such a way as to minimize other cognitive processes, such as learning, that might confound the interpretation of neural activity related to decision-making. Choices are randomized, independent of one another and, in humans, frequently trial-unique. However, even with these precautions in place, subjects are still able to learn. They are learning the range and average value of the choices that the experimenter might present. Consequently, although activity during the choice may reflect predictions about the outcome of the choice alternatives, it could equally reflect a prediction error, encoding the current options relative to the other potential choices the subject might have expected. For instance, if a subject has extensive experience with three equally probable choices valued at 0, 1, and 2, the average value of a choice in this experiment is 1. An offered choice of 2 is better than expected and could produce a prediction error at the time of the offer. Furthermore, in the typical decision-making experiment, outcome values and prediction errors are often strongly correlated. That is, a highly valued outcome is likely to be better than average and generate a large prediction-error relative to a second option where both value and prediction error might be smaller.

Figure 3 illustrates this point graphically. In this example task, the subject is presented with two stimuli on each trial (S_R and S_L), indicates his choice with a response (right or left arrows) and receives an outcome (*O*; **Figure 3A**). The value of S_R and S_L, the value of the outcome, and the prediction errors are represented by the height of colored bars (**Figure 3B**). Note that we have drawn prediction-error activity as it would appear in neuronal activity: computationally, events that are worse than expected should generate a negative prediction error, but neurons cannot have a negative firing rate. Thus, prediction errors are encoded relative to the neuron's mean or baseline firing rate (although it is not trivial to determine such a baseline in a high-level cognitive area such as prefrontal cortex). On trial *N*, the subject is presented with two low value stimuli and its choice (S_L) unexpectedly yields a large reward (green). The outcome generates a large positive prediction error (orange) because it was better than expected. However, neurons encoding prediction-errors could respond to the presentation of the reward-predicting stimuli as well as the receipt of the rewarding outcome. This is illustrated as a prediction error during the choice phase. In trial *N*, the choice prediction error is low because the values of the stimuli are low relative to other stimuli in the set. On trial $N + 1$, the subject is presented with two higher value stimuli, chooses S_R and unexpectedly receives a small reward. In this case, the choice prediction error is high, because S_R was expected to yield a large reward, however the outcome was worse than expected, leading to a negative prediction error during the outcome phase. Finally, on trial $N + 2$, the subject is presented with a high and a low value stimulus, chooses S_R and receives a large reward as expected. Here the choice prediction error is high, because the subject is given the option of a high valued stimulus, and there is no outcome prediction error (or the height of the bar is about at "baseline") because the outcome was fully predicted. From this illustration, it is evident that if you were to focus solely on neuronal activity during the choice phase you would not be able to differentiate neurons encoding prediction errors from those encoding the value of the chosen stimulus. Yet these signals have very different implications for the larger question of how the brain computes value-based decisions.

A prominent role for ACC in the encoding of learning signals is consistent with the dopaminergic input that this region receives. All areas of frontal cortex receive dopaminergic input, but it is particularly heavy in ACC (Williams and Goldman-Rakic, 1993). Furthermore, while dopamine signals have a very short latency (typically <100-ms from the onset of a reward or reward-predictive stimulus) ACC signals evolve over a longer timeframe. We found that the median time of ACC neurons to encode the amount of reward predicted by a stimulus was 230-ms (Kennerley and Wallis, 2009a). This would also be consistent with the dopaminergic input into ACC being responsible for the prediction errors that are observed there. However, we also note that the theory that dopamine neurons encode prediction errors is not without controversy. For example, there is debate as to whether prediction-error activity in dopamine neurons is a cause or consequence of value learning (Berridge, 2007). Further, some authors have suggested that responses of dopamine neurons are too rapid to encode prediction errors and instead respond to sensory properties of unexpected stimuli, and true prediction-error encoding should occur with longer latencies, in higher cortical areas (Redgrave and Gurney, 2006). These ideas raise the possibility that prediction errors could initially be computed in ACC during learning and then used to train up the short latency dopamine responses.

NEUROPHYSIOLOGICAL PROPERTIES OF OFC

With regard to OFC, a broad consensus seems to be emerging that OFC neurons encode value predictions rather than prediction errors (Roesch et al., 2010). We found no evidence of prediction-error signals in OFC in monkeys using the same task in which we detected prediction errors in ACC (Kennerley and Wallis, in press). Although OFC neurons encoded whether or not a reward occurred, there was little evidence that this signal was influenced by the animal's prior expectancy of receiving the reward. In humans, subjects have been required to bid on food items while simultaneously winning or losing money, thereby enabling prediction errors to be uncorrelated from value signals (Hare et al., 2008). fMRI revealed that OFC activity correlated with value while ventral striatal activity correlated with prediction errors. In rats performing an odor-guided task, OFC neurons encoded predictions but not prediction errors (Roesch et al., 2006), while the opposite was true for dopamine neurons (Roesch et al., 2007).

Anatomically, OFC is in an ideal position to encode the reward value of sensory stimuli. It receives input from high-level sensory

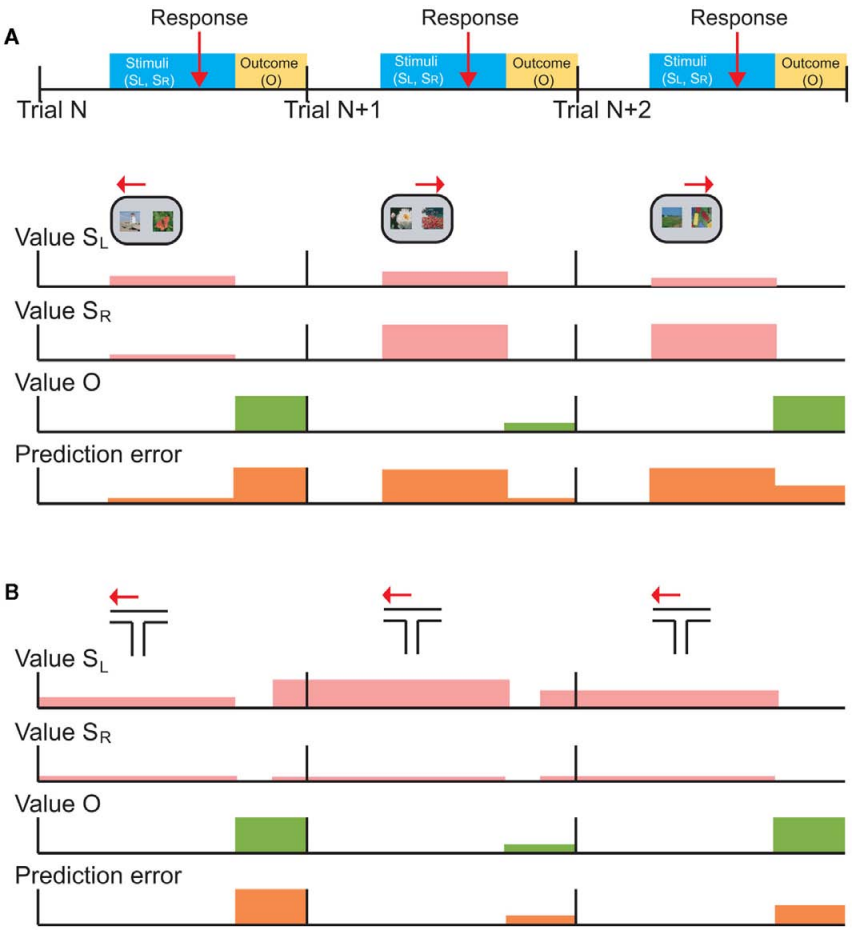

FIGURE 3 | Schematic depictions of typical choice tasks for primates and rodents are shown with the putative neuronal signals that those tasks should generate. (A) The temporal occurrence of behavioral events common to both tasks. On each trial (starting at the vertical black bars), the subject is presented with a choice between left (S_L) and right (S_R) stimuli, makes a response (red arrow), and receives an outcome (yellow shading). **(B)** Choice task typical in monkeys or humans, in which the subject is presented with the choice of two visual stimuli, S_L and S_R, selects one (left or right arrows), and then receives an outcome. The rows with pink bars show hypothetical learned values of S_L and S_R. A typical choice task conducted in humans and primates uses well learned stimuli from a larger set of reward-predictive stimuli, so the depicted values are shown as if they are well-known. The height of the bars indicates the degree of value, so that S_L has a slightly higher value than S_R on trial *N*, and so forth. The following two rows show the value of the actual outcome (Value *O*) and prediction-errors generated throughout the trial. A prediction error can be generated at the time of the choice, since the subject does not know specifically which choice will be presented. This choice prediction error is the difference between the value of the presented options, and the average value of the complete set of possible options. **(C)** A typical choice task conducted in rodents, in which the animal chooses between one of two arms in a T-maze, and receives an outcome. In this case, the same choice is effectively presented on every trial, so value predictions for S_L and S_R can be updated at the time of outcome receipt (green). This is shown as value predictions (pink) updating prior to the start of the next trial (i.e., shaded bars are shifted to the left). Furthermore, there is no choice prediction error because each trial consists of the same two choice options.

areas (Carmichael and Price, 1995b) as well as limbic structures responsible for processing rewards, such as the amygdala and hypothalamus (Carmichael and Price, 1995a). In addition, posterior OFC is responsible for the integration of taste and smell (Rolls and Baylis, 1994). Finally, OFC neurons encode the amount of reward predicted by a stimulus quickly, typically within 200-ms of the presentation of the stimulus. This is significantly quicker than neurons in ACC (Kennerley and Wallis, 2009a) or lateral prefrontal cortex (Wallis and Miller, 2003). This suggests that OFC neurons could serve as a source of reward information for the rest of the frontal cortex and perhaps even for subcortical structures. Indeed, a recent study has examined the relationship between OFC and dopamine. The authors disconnected OFC from the dopaminergic system using a crossed inactivation procedure, and showed that the two needed to interact in order for rats to learn from unexpected outcomes (Takahashi et al., 2009). They suggested that OFC provides dopamine neurons with a prediction as to the expected outcome. The dopamine neurons can then use this information, along with information about the actual outcome, in order to calculate a prediction error.

An exception to the consensus that OFC neurons encode predictions is a study examining the ability of rats to learn a probabilistically rewarded T-maze, which found encoding of prediction errors in OFC at the time of reward delivery (Sul et al., 2010). It

is possible that this difference reflects a difference in functional anatomy between rodents and primates. Most recordings from OFC in primates focus on areas 11 and 13, dysgranular cortex that may not have a homolog in rodents (Wise, 2008). It is the posterior, agranular OFC in primates that is the likely homolog of rodent OFC, yet this OFC region is frequently neglected by primate neurophysiologists. Thus, it is possible that if primate neurophysiologists were to record from this posterior OFC region they would see prediction errors.

However, it is also possible that differences in the way in which choice behavior is tested between primates and rats may contribute to observed neurophysiological differences. In primates and humans, each trial typically involves a two-alternative choice between reward-predictive stimuli whose outcome contingencies have been previously learned and that are drawn from a larger set of possible reward-predictive stimuli (e.g., **Figure 3B**). Thus, at the time of reward delivery a prediction error can be calculated, but the subject cannot make any specific predictions about the next trial, since it does not know which choice will be presented next. In contrast, rodents are typically tested in a learning situation involving the same two-alternative choice on every trial. For example, in the T-maze task the two alternatives are the right or left goal arms; in a task requiring nose-pokes, alternatives might be right or left ports. This means that at the time of reward delivery, not only can the rat calculate a reward prediction error, but it can also represent value predictions about the next trial.

The T-maze task is illustrated in **Figure 3C**. On the first trial, the subject selects a low value arm (S_L) and unexpectedly receives a large reward. The subject can immediately update the value of this arm for the next trial. On trial $N + 1$, the subject repeats this choice (S_L) and unexpectedly receives a small reward. The subject again updates its estimate of the value of this arm for the next trial, in this case decreasing its estimate of the value. Note that in this situation, prediction-errors generated by the outcome can overlap with the predictions for the next trial. These signals should be distinguishable during learning: as performance improves, predictions will begin to accurately reflect the value of the choice while prediction errors will tend toward zero. However, neuronal representations of stimulus values might change for reasons other than learning, for example due to adaptation (Padoa-Schioppa, 2009) or satiation (Bouret and Richmond, 2010).

This raises the question as to why other rodent studies did not see the same type of activity in OFC, since they also used the same two-alternative choice (Roesch et al., 2006). A key difference is that in this study rats were only given a free choice on about one-third of the trials. On the other two-thirds of the trials they were forced to choose one of the alternatives. This makes the task more similar to primate choice tasks, in that the rat is unable to predict the value of the next trial. In this situation, rat OFC neurons did not encode any signal that looked like a prediction error at the time of reward delivery, raising the possibility that these signals are actually related to predictions about the next trial.

SUMMARY

Across a broad range of studies OFC activity appears most consistent with encoding value predictions, and ACC activity appears most consistent with value prediction errors. In theory, there should be little problem in separating these two types of signal in the choice situation. The subject is faced with a choice, makes its selection and receives an outcome. At the time of choice, neurons should encode a prediction regarding the value of the potential outcomes. At the time of the outcome, neurons should encode a prediction-error reflecting the discrepancy between the actual outcome and the prediction. In practice, however, things are more problematic. Prediction errors can be generated at the time of the choice, because the subject is comparing the choice with other potential choices that may have occurred, and predictions can be generated at the time of the outcome if the subject is going to experience the same choice on the next trial. It is important to recognize that trials in behavioral tasks do not take place in isolation and computational processes occurring within the temporal limits of one trial could reflect the influence of past or upcoming trials.

SALIENCY AND ITS EFFECTS ON ATTENTION, AROUSAL, AND MOTOR PREPARATION

Valuable items are salient. Even under experimental conditions, a high value item can trigger a variety of processes linked to its saliency, including an increase in attention, arousal, and motor preparation (Maunsell, 2004; Luk and Wallis, 2009). These processes, in turn, can have clear behavioral consequences. For example, offers of larger or more immediate rewards increase motivation and attentiveness to tasks, resulting in fewer incorrect responses and fewer errors in task execution, such as breaks in visual fixation (Kennerley and Wallis, 2009b). Larger rewards enhance preparation for response execution, so that motor responses are faster when more desirable outcomes are at stake (Kawagoe et al., 1998; Leon and Shadlen, 1999; Hassani et al., 2001; Kobayashi et al., 2002; Roesch and Olson, 2003). Rewards generate psychophysiological measures of arousal such as changes in galvanic skin conductance (Bechara et al., 1996) and heart rate and blood pressure (Braesicke et al., 2005). Finally, value can even correlate with muscle tone in the neck and jaw as recorded by EMG, likely a result of arousal or preparation for ingestive behaviors (Roesch and Olson, 2003, 2005). These are potent demonstrations that behavioral and physiological responses can be tightly coupled to value, and neural encoding of these effects could be indistinguishable from value encoding. Indeed, at the neural level salient items have widespread effects. There are stronger representations of more valuable cues in nearly all cortical areas considered, even primary sensory areas (Pantoja et al., 2007; Pleger et al., 2008; Serences, 2008), likely because of the heightened attentional and motivational salience of valuable items. However, interpretations become difficult when multiple signals correlating with value are found in frontal regions. For instance, neural representations of cognitive processes like working memory in ventrolateral PFC are influenced by reward magnitude (Kennerley and Wallis, 2009b) even though a lesion of lateral PFC has no effect on value-based decisions (Baxter et al., 2009). Analysis of latencies to respond to valuable stimuli found that OFC encodes value earlier than lateral PFC, suggesting that value information is passed from OFC to other PFC regions (Wallis and Miller, 2003). While these lateral PFC signals likely serve important functions, such as allocating cognitive resources appropriately, it is important to distinguish these downstream effects from value calculations themselves.

The only way to dissociate putative value signals from signals relating to saliency is to use stimuli or events that are aversive. Aversive stimuli (e.g., electric shock) have a negative value in that they negatively reinforce actions and can motivate avoidance behavior. True value signals should distinguish appetitive stimuli (rewards) and aversive stimuli (punishments). In contrast, saliency is associated with expectation of either punishment or reward, so that neural responses correlating with salience should be similar under rewarding and punishing conditions (Lin and Nicolelis, 2008).

Before we consider how these ideas have been applied to the interpretation of neuronal data, there are two additional issues we should consider. First, it is not necessarily the case that rewards and punishments will be encoded on the same scale. One neuronal population could encode the value of appetitive stimuli while a separate population could encode the value of aversive stimuli. Indeed, two prominent theories regarding the organization of value information have posited separate representations of appetitive and aversive information. One theory suggests that positive and negative outcomes are encoded by medial and lateral OFC respectively (Kringelbach and Rolls, 2004; Frank and Claus, 2006), while another argues that this distinction lies between OFC and ACC respectively (Aston-Jones and Cohen, 2005). Though there are data to support and contradict both theories, in principle, it is possible that different neural circuits represent different valences. In contrast, saliency signals by definition cannot discriminate the valence of the stimulus: if they did, they would be operationally identical to value signals.

There are also psychological reasons why rewards and punishments might not be encoded by the same neuronal population. Whereas subjects work to obtain rewards, they work to avoid aversive outcomes. This introduces a key paradox of avoidance learning: as learning progresses, there is less and less exposure to the reinforcing stimulus. By standard reinforcement learning theory, this situation should produce extinction, yet robust avoidance learning is readily obtained (Solomon et al., 1953). The influential two-process theory (Mowrer, 1947) suggests that aversively conditioned cues come to elicit a negative emotional state through Pavlovian conditioning. Responses that terminate the cue are then reinforced by the reduction of the negative emotional state. A similar two-process theory has been postulated to underlie learning about rewards (Rescorla and Solomon, 1967). In this case, the cues activate positive emotional states, which in turn elicit responses toward the desired outcome. Thus, if learning requires the activation of specific emotional states, it is possible that different neuronal populations will be responsible for the representation of different emotional states rather than a single neuronal population encoding value along a common scale.

A second issue relates to the conflation of costs with aversive stimuli. Motivated behavior typically accrues certain costs, such as the time and effort involved in acquiring a desired outcome, or the risk that the desired outcome will not be obtained. Although costs influence behavior (e.g., all other things being equal the subject will choose the outcome whose acquisition involves the lowest costs), the desired outcome, not the cost, provides motivation for behavior. The subject's goal is to acquire an appetitive stimulus or avoid an aversive stimulus, and the cost is a necessary evil in obtaining that goal.

DISSOCIATING VALUE AND SALIENCY SIGNALS

The goal of dissociating value and saliency signals motivated an experiment in which hungry humans were shown a variety of food items and asked whether they would like to eat them (Litt et al., 2011). They provided ratings of "Strong no," "No," "Yes," or "Strong yes." The food items were chosen to be appetitive (e.g., potato chips) or aversive (e.g., baby food). BOLD signals in rostral ACC and medial OFC showed a positive correlation with the value of the item, lowest for items rated "Strong no" and highest for "Strong yes" (**Figure 4A**). In contrast, areas such as the supplementary motor area (SMA) and the insula consistently showed higher activity for "Strong" responses, irrespective of whether they were a "Strong yes" or a "Strong no," consistent with a saliency-related signal (**Figure 4B**).

However, there is an important caveat to the interpretation of neuroimaging results. Neuroimaging studies tend to largely localize value signals to the ventral part of the medial wall of prefrontal cortex, yet single neurons encoding value are found throughout frontal cortex (Wallis and Kennerley, 2010). This suggests that neuroimaging methods are underestimating the extent of frontal cortex involved in valuation processes. A possible explanation for this lies in the fact among value encoding neurons, those that increase their firing rate as values increase are found in approximately equal numbers as those that increase their firing rate as values decrease (Kennerley and Wallis, 2009a; Kennerley et al., 2009; Padoa-Schioppa, 2009). It is possible that such signals could cancel one another out when averaged together in the BOLD signal. Support for this idea has come from recent studies that have directly compared the BOLD response to underlying neuronal activity in area MT (Lippert et al., 2010). Neuronal activity (whether measuring action potentials or local field potentials) shows parametric tuning related to the direction of motion of a visual stimulus. However, the BOLD response is evoked by stimuli moving in any direction, precisely as though tuned populations were being added together thereby masking the tuning. Consequently, it is important to dissociate value and saliency signals at the single-unit level.

The first study that attempted to systematically dissociate these two signals required a monkey to choose between stimuli that were associated either with different amounts of juice or different lengths of a "time-out" (the monkey had to simply sit and wait a designated amount of time until the next trial started and did not receive any juice; Roesch and Olson, 2004). Both OFC and premotor neurons tended to increase firing rate as expected rewards increased, appearing to code the value of different reward magnitudes. However, only OFC neurons decreased firing as expected punishment increased, and thus scaled with the value of both positive and negative outcomes. Premotor neurons, in contrast, increased firing to increasing penalties, suggesting that they code information related to motivation, arousal, or motor preparation. Although this study suggests that OFC neurons encode rewards and punishments along a single scale, there is an alternative explanation. It is not clear that a "time-out" is necessarily a punisher and could instead be construed as a cost that must be overcome in order to obtain reward on subsequent trials. Indeed, several studies suggest that OFC may be responsible for integrating reward information with temporal costs (Roesch and Olson, 2005; Rudebeck et al., 2006; Kable and Glimcher, 2007).

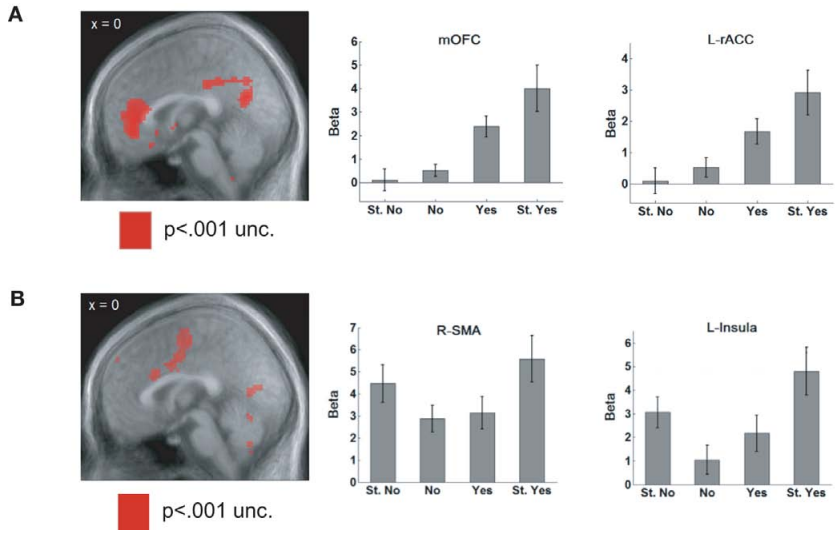

FIGURE 4 | (A) When rating appetitive and aversive foods, BOLD signals in rostral ACC and medial OFC showed a positive correlation with the value of the item. They showed the weakest activity for a "Strong no" response and the activation steadily increased as the rating of the item became more positive. **(B)** Areas such as the supplementary motor area (SMA) and the insula were activated by saliency, showing higher activity for "Strong" responses, irrespective of whether they were a "Strong yes" or a "Strong no." Adapted from Litt et al. (2011, pp. 98–99) by permission of Oxford University Press.

Subsequent studies have explored OFC responses to cues that predict more unambiguous punishers such as electric shock (Hosokawa et al., 2007) or an air puff to the face (Morrison and Salzman, 2009). Notably, there was evidence that single OFC neurons encoded the appetitive and aversive outcomes along a single scale. For example, they would show a strong response to a large reward, a weaker response to a small reward and an even weaker response to the aversive stimulus. Importantly, there was no evidence of a functional topography of responses. Neurons that showed stronger responses to aversive events appeared to be randomly interspersed with neurons that showed stronger responses to appetitive events (Morrison and Salzman, 2009), casting doubt on the theory that appetitive encoding is located more medially than aversive coding (Kringelbach and Rolls, 2004; Frank and Claus, 2006). In this study, cue–outcome associations were conditioned in a Pavlovian manner, eliminating decision-making from the task design. It will be interesting in future studies to examine how these findings extend to choice behavior.

GAINS AND LOSSES

Our discussion so far has focused on positive punishment: punishing behavior by presenting an aversive stimulus. However, there is a second class of punishment, negative punishment, in which a subject is punished by the removal of an appetitive stimulus. Most studies of valuation in humans involve winning and losing money (Breiter et al., 2001; Knutson et al., 2005), which is a form of negative punishment, in that losing money consists of the removal of an appetitive stimulus. Critically, negative punishment requires the use of secondary reinforcement. This is because once a subject has received a primary reinforcement, such as a shock or a food reward, there is no way to take it back. In contrast, a secondary reinforcer, such as money, can be removed before the subject has had the ability to consume it.

Few studies in animals have involved negative punishment. One exception is a study that examined the ability of animals to play a competitive game for tokens (Seo and Lee, 2009). Monkeys played against a computer opponent, trying to guess which of two targets the computer would choose on each trial. If both subject and computer chose the same target, the subject had a high probability of gaining a token; if they chose different targets there was the risk of losing a token. For every six tokens won, the animal received juice as a primary reward. Although the optimal approach to the task was to choose randomly, monkeys tended to modify their behavior based on their previous choices, demonstrating that gains and losses affected choice behavior. As such, individual neurons in multiple cortical areas, including dorsomedial PFC, dorsolateral PFC, and dorsal ACC, had differential responses to gains and losses, the first time the effects of negative punishment have been seen at the single neuron level. Furthermore, individual neurons showed opposing responses to gains and losses relative to neutral outcomes. For example, they might show a strong response to a gain, a weaker response to a neutral outcome, and little or no response to a loss indicating that reward and punishment may be coded along a single value dimension.

Nevertheless, this use of gains and losses of conditioned reinforcers remains an exception in the animal literature. Most animal studies do not include punishment, and if they do it is typically positive punishment. The precise implications of this disconnect between human and animal studies remains unclear, but recent findings suggest that different regions of OFC may be responsible for the encoding of primary and secondary reinforcement. For example, monetary reward, a secondary reinforcer, activates more anterior regions of OFC than erotic pictures, a primary reinforcer (Sescousse et al., 2010). Furthermore, aversive conditioning based on monetary loss does not activate the amygdala, which is highly interconnected with OFC, while the same conditioning based on

electric shock does (Delgado et al., 2011), suggesting that OFC may also respond differentially to positive and negative punishment. Consequently, different conclusions may be reached by investigators studying decision-making in animals or humans, not because of a genuine species difference, but rather because of a difference in the way the species are tested behaviorally. In future neurophysiology studies it will be important to bring clarity to these issues by comparing single neuron responses in both OFC and ACC to primary and secondary reinforcement.

SUMMARY

In sum, measures of value and saliency signals are highly correlated unless tasks employ both rewarding and punishing outcomes. Aversive events can include either primary punishment, such as electric shock, or negative punishment, such as the loss of a valuable item. In either case they should be distinguished from a cost that accompanies reward, since it is unknown whether costs and punishments are coded similarly at the neural level. A number of studies have now successfully disambiguated value from saliency signals, and found that ACC and OFC activity correlates with value, not saliency. It is important to keep pursuing these types of distinctions, since they have significant implications for our interpretation of neuronal activity.

CONCLUSION

It has been over 30 years since the first studies determined that frontal neurons showed responses that predicted reward outcomes (Niki and Watanabe, 1976; Rosenkilde et al., 1981). In the ensuing decades, researchers have made a great deal of progress in understanding how positive and negative outcomes can influence choices. Formal behavioral models have been adopted, which, in turn, have allowed for a more quantitative analysis of neuronal responses. In this paper, we have outlined a number of challenges confronted when assessing the neural correlates of these behavioral models. We hope that this will prove useful for disambiguating the contribution of different neuronal populations to choice behavior.

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Impact of size and delay on neural activity in the rat limbic corticostriatal system

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A number of factors influence an animal's economic decisions. Two most commonly studied are the magnitude of and delay to reward. To investigate how these factors are represented in the firing rates of single neurons, we devised a behavioral task that independently manipulated the expected delay to and size of reward. Rats perceived the differently delayed and sized rewards as having different values and were more motivated under short delay and big-reward conditions than under long delay and small reward conditions as measured by percent choice, accuracy, and reaction time. Since the creation of this task, we have recorded from several different brain areas including, orbitofrontal cortex, striatum, amygdala, substantia nigra pars reticulata, and midbrain dopamine neurons. Here, we review and compare those data with a substantial focus on those areas that have been shown to be critical for performance on classic time discounting procedures and provide a potential mechanism by which they might interact when animals are deciding between differently delayed rewards. We found that most brain areas in the cortico-limbic circuit encode both the magnitude and delay to reward delivery in one form or another, but only a few encode them together at the single neuron level.

Keywords: discounting, value, dopamine, orbitofrontal, striatum, amygdala, substantia nigra

INTRODUCTION

Animals prefer an immediate reward over a delayed reward even when the delayed reward is more economically valuable in the long run. In the lab, the neural mechanisms underlying this aspect of decision-making are often studied in tasks that ask animals or humans to choose between a small reward delivered immediately and a large reward delivered after some delay (Herrnstein, 1961; Ainslie, 1974; Thaler, 1981; Kahneman and Tversky, 1984; Rodriguez and Logue, 1988; Lowenstein, 1992; Evenden and Ryan, 1996; Richards et al., 1997; Ho et al., 1999; Cardinal et al., 2001; Mobini et al., 2002; Winstanley et al., 2004b; Kalenscher et al., 2005; Kalenscher and Pennartz, 2008; Ballard and Knutson, 2009; Figner et al., 2010). As the delay to the large reward becomes longer, subjects tend to start discounting the value of the large reward, biasing their choice behavior toward the small, immediate reward (temporal discounting). This choice behavior is considered to be impulsive because over the course of many trials it would be more economical to wait for the larger reward. Impulsive choice is exacerbated in several disorders such as drug addiction, attention-deficit/hyperactivity disorder, and schizophrenia, altering the breakpoint at which subjects abandon the large-delayed reward for the more immediate reward (Ernst et al., 1998; Jentsch and Taylor, 1999; Monterosso et al., 2001; Bechara et al., 2002; Coffey et al., 2003; Heerey et al., 2007; Roesch et al., 2007c; Dalley et al., 2008). Although considerable attention has been paid to the neuroanatomical and pharmacological basis of temporally discounted reward and impulsivity, few have examined the neural correlates involved. Specifically, few have asked how delays impact neural encoding in brain areas known to be involved in reinforcement learning and decision-making, and how that encoding might relate to less abstract manipulations of value such as magnitude. To address this issue we developed an inter-temporal choice task suitable for behavioral recording studies in rats (Roesch et al., 2006, 2007a,b, 2009, 2010b; Takahashi et al., 2009; Calu et al., 2010; Stalnaker et al., 2010; Bryden et al., 2011).

In this task, rats were trained to nosepoke into a central odor port. After 0.5 s, one of three odors was presented. One odor signaled for the rat to go left (forced-choice), another signaled go right (forced-choice), and the third odor signaled that the rat was free to choose either the left or right well (free-choice) to receive liquid sucrose reward. The two wells were located below the odor port as illustrated in **Figure 1B**. After responding to the well, rats had to wait 0.5 or 1–7 s to receive reward, depending on trial type (**Figure 1A**). The task was designed to allow for equal samples of left and rightward responses (forced-choice) while at the same time having a direct measure of the animal's preference (free-choice). In addition, use of free- and forced-choice trials has allowed us to determine whether the brain processes free-choice differently than forced instrumental responding and whether or not observed neural correlates reflect sensory or motor processing.

At the start of each session, we shifted the rats' response bias to the left or to the right by increasing the delay preceding reward delivery in one of the two fluid wells (1–7 s). During delay blocks, each well yielded one bolus of 10% sucrose solution. After ∼60–80 trials, the response direction associated with the delayed well switched unexpectedly. Thus, the response direction that was associated with a short delay became long, whereas the response direction associated with the long delay in the first block of trials

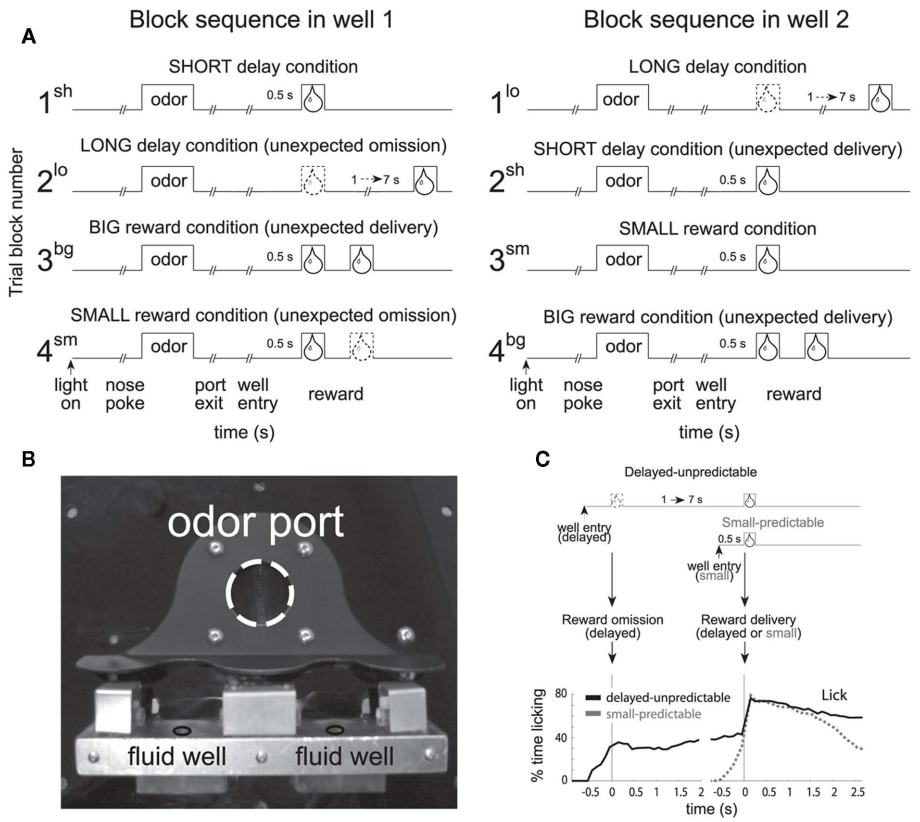

FIGURE 1 | Size and Delay Behavioral Choice Task. (A) Figure shows sequence of events in each trial in 4 blocks in which we manipulated the time to reward or the size of reward. Trials were signaled by illumination of the panel lights inside the box. When these lights were on, nosepoke into the odor port resulted in delivery of the odor cue to a small hemicylinder located behind this opening. One of three different odors was delivered to the port on each trial, in a pseudorandom order. At odor offset, the rat had 3 s to make a response at one of the two fluid wells located below the port. One odor instructed the rat to go to the left to get reward, a second odor instructed the rat to go to the right to get reward, and a third odor indicated that the rat could obtain reward at either well. At the start of each recording session one well was randomly designated as short (a 0.5 s delay before reward) and the other long (a 1 to 7 s delay before reward) (block 1). In the second block of trials these contingencies were switched (block 2). In blocks 3 and 4 delays were held constant (0.5 s) and reward size was manipulated. sh = short; bg = big; lo = long; sm = small; **(B)** Picture of apparatus. **(C)** Percent licking behavior averaged over all recording sessions during trials when a small reward was delayed versus when a small reward was delivered after 0.5 s. Licking is aligned to well entry (left) and reward delivery (right). Adapted from (Roesch et al., 2006, Roesch et al., 2007b, Takahashi et al., 2009).

became short. During delay blocks, the intertrial intervals were normalized so that the length of short and long delay trials were equal, thus there was no overall benefit to choosing the short delay, but as we will describe, rats did so regardless.

These contingencies continued for ∼60–80 trials at which time both delays were set to 0.5 s and the well that was associated with the long delay, now produced a large reward (two to three boli). These contingencies were again switched in the fourth block of trials. Trial block switches were not cued, thus animals had to detect changes in reward contingencies and update behavior from block to block.

It is important to emphasize that reward size and delay were varied independently, unlike common delay discounting tasks. Whereas other studies have investigated the neuronal coding of temporally discounted reward in paradigms that have manipulated size and delay simultaneously, our task allows us to dissociate correlates related to size and delay to better understand how each manipulation of value is coded independently from the other. As we will show below, rats prefer or value short over long delays to reward and large over small reward as indicated by choice performance. We felt it was necessary to dissociate size correlates from delay correlates because certain disorders and brain manipulations have been shown to impair size and delay processing independently, sometimes in an opposing manner (Roesch et al., 2007c). Although we do not manipulate the size of the reward along with the length of the delay preceding reward delivery in the traditional sense, any effects on choice behavior and neural firing must be dependent on the delay and reflect how time spent waiting for a reward reduces the value of reward. The depreciation of the reward value due to delay has been referred to as the temporally discounted value of the reward (Kalenscher and Pennartz, 2008).

In each of the studies that we will describe below, rats were significantly more accurate and faster on high value reward trials (large reward and short delay) as compared to low value reward trials (small reward and long delay) on forced-choice trials (Roesch et al., 2006, 2007a,b, 2009, 2010b; Takahashi et al., 2009; Calu et al., 2010; Stalnaker et al., 2010; Bryden et al., 2011). On free-choice trials, rats chose high over low value and switched their preference

rapidly after block changes. Thus, rats discounted delayed rewards, choosing it less often and working less hard to achieve it. Preference of immediate reward over delayed reward was not significantly different than preference of the large over small reward.

In addition, behavioral measures have illustrated that delayed rewards were less predictable than more immediate rewards in this task (Takahashi et al., 2009). Even after learning, the rats could not predict the delayed reward with great precision. Licking increased rapidly prior to the small, more immediate reward and showed no change prior to delivery of the delayed small reward (**Figure 1C**; Takahashi et al., 2009). Instead, rats' licking behavior increased around 0.5 s after well entry on delayed trials (**Figure 1C**) corresponding to the time when delivery of immediate reward would have happened in the preceding block of trials (**Figure 1C**). Thus, rats anticipated delivery of immediate reward, even on long delay trials and, although they knew that the delayed reward would eventually arrive, they could not predict exactly when. Similar findings have been described in primates (Kobayashi and Schultz, 2008).

In this article, we review neural correlates related to performance of this task from several brain areas, with a stronger focus on those areas that have been shown to disrupt behavior on standard delay discounting tasks after lesions, inactivation, or other pharmacological manipulations (Cardinal et al., 2004; Floresco et al., 2008).

ORBITOFRONTAL CORTEX

Impulsive choice in humans has long been attributed to damage of orbitofrontal cortex (OFC), but the role that OFC plays in inter-temporal choices remains unclear. OFC lesions decrease and increase discounting functions depending on experimental design and lesion location (Mobini et al., 2002; Winstanley et al., 2004b; Rudebeck et al., 2006; Winstanley, 2007; Churchwell et al., 2009; Sellitto et al., 2010; Zeeb et al., 2010; Mar et al., 2011). From these data it has been clear that OFC is involved in inter-temporal choice suggesting that it must carry information related to the length of delay preceding the delivery of reward.

To investigate how delay and size were encoded in OFC, we recorded from single neurons while rats performed the task described above (Roesch et al., 2006). Consistent with previous work, lateral OFC neurons fired in anticipation of delayed reward. As illustrated in **Figure 2A**, activity of many single neurons continuously fired until the delayed reward was delivered, resulting in higher levels of activity for rewards that were delayed (**Figure 2A**; bottom; gray).

Surprisingly, the majority of OFC neurons in our study did not show this pattern of activity (Roesch et al., 2006). Most OFC neurons did not maintain firing across the delay as illustrated by the single cell example in **Figure 2B**. Under short delay conditions, this neuron fired in anticipation of and during the delivery of immediate reward (top; black). When the reward was delayed (gray), activity declined until the delayed reward was delivered, and thus, did not bridge the gap between the response and reward as in the previous example (**Figure 2A**). Interestingly, activity seemed to reflect the expectation of reward by continuing to fire when the reward would have been delivered on previous trials (i.e., 0.5 s after the response). This old expectancy signal slowly dissipated with learning (**Figure 2B**).

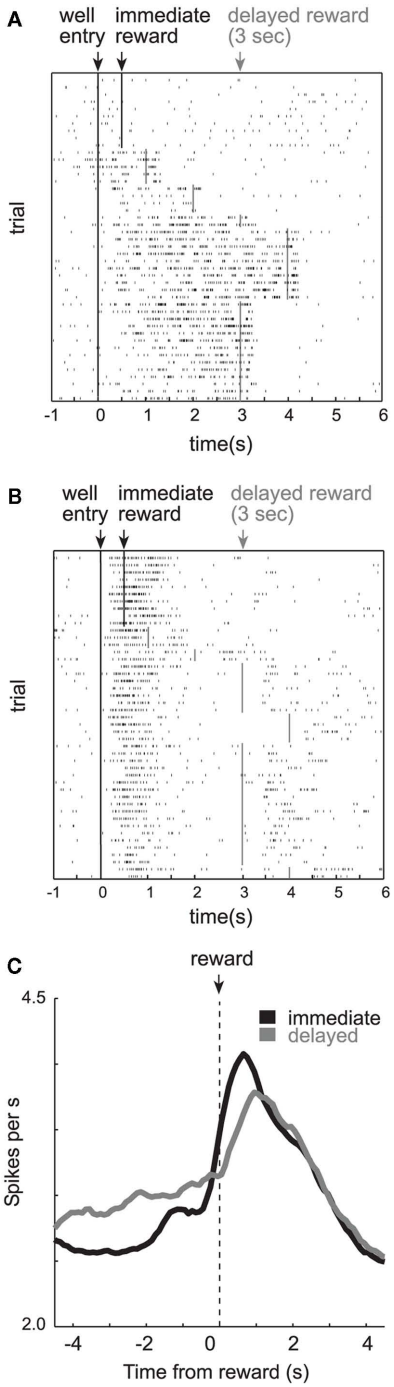

FIGURE 2 | Orbitofrontal cortex (OFC). (A) Single cell example of reward expectancy activity. **(B)** Single cell example of a neuron that exhibits reduced activity when rewards are delayed compared to when rewards are delivered immediately (black). Activity is plotted for the last 10 trials in a block in which reward was delivered in the cell's preferred direction after 0.5 s (black) followed by trials in which the reward was delayed by 1–4 s (gray). Each row represents a single trial, each tick mark represents a single action potential and the colored lines indicate when reward was delivered. **(C)** Averaged firing rate of all OFC neurons that fired significantly ($p < 0.05$) more strongly during a 1-s period after reward delivery compared to baseline (adapted from Roesch et al., 2006).

Thus, it appears that although many OFC neurons maintained representations of the reward across the delay, most did not. Overall activity across the population of reward-responsive neurons was stronger during delivery of immediate reward as compared to delayed reward (**Figure 2C**). These changes in firing likely had a profound impact on inter-temporal choice. Indeed, firing of OFC neurons was correlated with the tendency for the rat to choose the short delay on future free-choice trials (Roesch et al., 2006, 2007a).

We suspect that these two types of signals play very different roles during performance of standard delay discounting paradigms (Roesch et al., 2006, 2007a). Reward expectancy signals that maintain a representation of the delayed delivery of reward (**Figure 2A**) might be critical for facilitating the formation of associative representations in other brain regions during learning. For example, it has been shown that input from OFC is important for rapid changes in cue–outcome encoding in basolateral amygdala (Saddoris et al., 2005) and prediction error signaling in DA neurons in ventral tegmental area (VTA). Loss of cue–outcome encoding in downstream areas after OFC lesions may be due to the loss of expectancy signals generated in OFC (Schoenbaum and Roesch, 2005). If the purpose of expectancy signals in OFC is to maintain a representation of the reward when it is delayed so that downstream areas can develop cue or response–outcome associations, then animals with OFC lesions would be less likely to choose those cues or responses when they result in the delayed reward. This interpretation is consistent with reports that lesions of OFC can cause more impulsive responding (Rudebeck et al., 2006).

The majority of OFC neurons fired more strongly for immediate reward (**Figure 2B**). These neurons likely represent when an immediate reward is or is about to be delivered. When the reward is delayed, this expectation of immediate reward is violated and a negative prediction error is generated in downstream areas. Negative prediction error signals would subsequently weaken associations between cues and responses that predict the now delayed reward. These changes would drive behavior away from responses that predict the delayed reward. Elimination of this signal could make animals less likely to abandon the delayed reward as has been shown in previous studies (Winstanley et al., 2004b).

To add to this complexity, a recent study suggests that different regions of OFC might serve opposing functions related to inter-temporal choice (Mar et al., 2011). In this study, Mar and colleagues showed that lesions of medial OFC make rats discount slower, encouraging responding to the larger delayed reward, whereas lateral OFC lesions make rats discount faster, decreasing preference for the larger delayed reward. How does this relate to our data? It suggests that neurons that bridge the gap during the delay preceding reward delivery might be more prominent in lateral OFC. This hypothesis is consistent with human imaging studies showing a positive correlation between OFC activation and preference for delayed reward (McClure et al., 2004, 2007; Hariri et al., 2006; Boettiger et al., 2007; Mar et al., 2011). These data also suggest that neurons that exhibit reduced activity for delayed reward, firing more strongly for immediate reward, might be more prominent in medial OFC. This hypothesis is consistent with human imaging studies showing that activation of medial OFC is positively correlated with preference of more immediate reward (McClure et al., 2004, 2007; Hariri et al., 2006; Mar et al., 2011). Future studies will have to examine whether this theory is true and/or if other signals might be involved in generating the opposing symptoms observed after medial and lateral OFC lesions.

Notably, a number of other prefrontal cortical areas are thought to be involved in processing delayed reward. Most of this work has come from humans and in studies examining neural activity in monkeys. For example, Kim et al. (2008) found that single neurons in monkey prefrontal cortex (PFC) were modulated by both expected size of and delay to reward in a task in which monkeys chose between targets that predicted both magnitude and delay. Human studies have backed these findings and have further suggested that PFC, unlike OFC, might be more critical in evaluating rewards that are more extensively delayed (e.g., months to years; McClure et al., 2004, 2007; Tanaka et al., 2004; Kable and Glimcher, 2007; Ballard and Knutson, 2009; Figner et al., 2010).

BASOLATERAL AMYGDALA

Much of the evidence we have described for the general role of OFC in anticipating future events and consequences can also be found in studies of amygdalar function, in particular, the ABL (Jones and Mishkin, 1972; Kesner and Williams, 1995; Hatfield et al., 1996; Malkova et al., 1997; Bechara et al., 1999; Parkinson et al., 2001; Cousens and Otto, 2003; Winstanley et al., 2004d). This is perhaps not surprising given the strong reciprocal connections between OFC and ABL and the role that ABL is proposed to play in associative learning. ABL also appears to play a critical role during inter-temporal choice. Rats with ABL lesions are more impulsive when rewards are delayed, abandoning the delayed reward more quickly than controls (Winstanley et al., 2004b; Cardinal, 2006; Churchwell et al., 2009; Ghods-Sharifi et al., 2009).

As in many studies, activity patterns observed in ABL during performance of our task were similar to those observed in OFC; neurons represented predicted outcomes at the time of cue presentation and in anticipation of reward (Roesch et al., 2010b). The two areas differed in that signals related to anticipated reward and delivery did not appear to be as reduced in ABL as they were in OFC when rewards were delayed. This is evident by comparing population histograms from both areas (OFC: **Figure 2C** versus ABL: **Figure 3A**). The counts of neurons that fired significantly more strongly for immediate reward did not outnumber the number of neurons that fired more strongly for delayed reward in ABL as they did in OFC.

Another difference between ABL and OFC was that neurons in ABL also fired more strongly when reward was delivered unexpectedly. For example, many ABL neurons fired strongly when the big-reward was delivered at the start of blocks 3 and 4 (**Figure 1A**). Although the mainstream view holds that amygdala is important for acquiring and storing associative information (LeDoux, 2000; Murray, 2007), these data and others like it have recently suggested that amygdala may also support other functions related to associative learning such as detecting the need for increased attention when reward expectations are violated (Gallagher et al., 1990; Holland and Gallagher, 1993b, 1999; Breiter et al., 2001; Yacubian et al., 2006; Belova et al., 2007; Tye et al., 2010). Consistent with this hypothesis, we have shown that activity during unexpected reward delivery and omission was

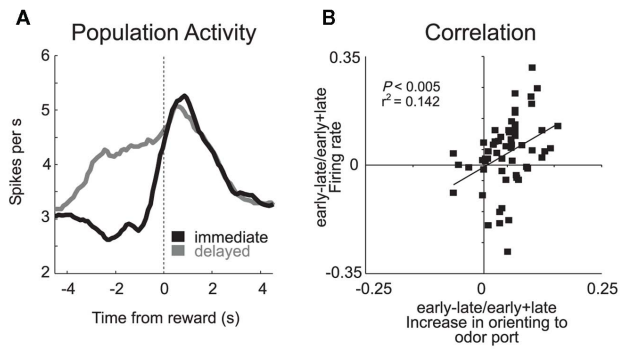

FIGURE 3 | Basolateral amygdala (ABL). (A) Average firing rate for all reward-responsive neurons in ABL on the last 10 trials during immediate (gray) and delayed (black) reward after learning. **(B)** Activity in ABL was correlated with odor port orienting as defined by the speed at which rats initiated trials after house light illumination during the first and last 10 trials in blocks 2–4. These data were normalized to the maximum and inverted. Error bars indicate SEM (adapted from Roesch et al., 2010b).

correlated with changes in attention that occur at the start of trial blocks (**Figure 3B**) and that inactivation of ABL makes rats less likely to detect changes in reward contingencies (Roesch et al., 2010b).

Unfortunately, it is still unclear what sustained activity during the delay represents in ABL. Sustained activity in ABL might reflect unexpected omission of reward, signaling to the rat to attend more thoroughly to that location so that new learning might occur. It might also serve to help maintain learned associations and/or to learn new associations when delays are introduced between responses and reward delivery. Consistent with this hypothesis, ABL lesions have been shown to reduce the selectivity of neural firing in OFC and ventral striatum (VS; Schoenbaum et al., 2003; Ambroggi et al., 2008). If ABL's role is to help maintain expectancies or attention across the gap between responding and delivery of delayed reward, then loss of this signal would increase impulsive choice as has been shown by other labs (Winstanley et al., 2004b).

Finally, it is worth noting that other parts of the amygdala might be critical for inter-temporal decision-making. Most prominent is the central nucleus of amygdala (CeA), which is critical for changes in attention or variations in event processing that occur during learning when rewards downshift from high to low value (Holland and Gallagher, 1993a,c, 2006; Holland and Kenmuir, 2005; Bucci and Macleod, 2007). We have recently shown that downshifts in value, including when rewards are unexpectedly delayed, increase firing in CeA during learning (Calu et al., 2010). Changes in firing were correlated with behavioral measures of attention observed when reward contingencies were violated, which were lost after CeA inactivation (Calu et al., 2010). Surprisingly, inactivation of CeA did not impact temporal choice in our task (Calu et al., 2010). This might reflect control of behavior via detection of unexpected reward delivery which happens concurrently with unexpected reward omission during each block switch. To the best of our knowledge, it is unknown how CeA lesions would impact performance on the standard small-immediate versus large-delayed reward temporal discounting task, but we suspect that rats would be less impulsive.

DOPAMINE NEURONS IN VENTRAL TEGMENTAL AREA

Manipulations of DA can either increase or decrease how much animals discount delayed reward (Cardinal et al., 2000, 2004; Wade et al., 2000; Kheramin et al., 2004; Roesch et al., 2007c); however, few studies have examined how DA neurons respond when rewards are unexpectedly delayed or delivered after long delay (Fiorillo et al., 2008; Kobayashi and Schultz, 2008; Schultz, 2010). As in previous work, unexpected manipulation of reward size in our task impacted firing of DA neurons in VTA. Activity was high or low depending on whether reward was unexpectedly larger (positive prediction error) or smaller (negative prediction error), respectively, and activity was high or low depending on whether the odor predicted large or small reward, respectively. Thus, consistent with previous work, the activity of DA neurons appeared to signal errors in reward prediction during the presentation of unconditioned and conditioned stimuli (Mirenowicz and Schultz, 1994; Montague et al., 1996; Hollerman and Schultz, 1998a,b; Waelti et al., 2001; Fiorillo et al., 2003; Tobler et al., 2003; Nakahara et al., 2004; Bayer and Glimcher, 2005; Pan et al., 2005; Morris et al., 2006).

DA neurons also signaled errors in reward prediction when rewards were delayed (Roesch et al., 2007b). Delivery of an unexpected immediate reward elicited a strong DA response (**Figure 4B**; immediate reward; red blotch; first 10 trials), which was subsequently replaced by firing to cues that predicted the short delay after learning (**Figure 4B**; last 10 trials). That is, activity was stronger at the end of the block (dashed blue line) than during the first several trials of that same block (solid blue line) just after odor presentation (**Figure 4C**). Overall, population activity was the strongest during cues that predicted the immediate reward (**Figures 4A–C**; Roesch et al., 2007b). Moreover, neurons that tended to fire more strongly for immediate reward also fired more strongly for cues that predicted large reward (**Figure 4E**).

When rewards were unexpectedly delayed, DA neurons were inhibited at the time when the reward should have arrived on short delay trials (**Figure 4D**; omitted reward; first 10 trials). Again, this negative prediction error signal transferred to cues that predicted the delayed reward after learning (**Figure 4D**; last 10 trials). That is, cue-related activity was still strong at the start of the block before the rat realized that the cue no longer signaled short delay. During odor sampling activity was the weakest when that cue signaled the longest delay (**Figure 4A**; 7 s; cue onset).

Finally, consistent with delayed rewards being unpredictable (**Figure 1C**), rewards delivered after long delay elicited strong firing (**Figure 4A**; 7 s; cue onset and **Figure 4D**; delayed reward). Activity after 2 s did not increase with each successive delay increase. This is likely due to rats updating their expectations as the delay period grew second by second. All of these findings are consistent with the notion that activity in midbrain DA signals errors in reward prediction.

Importantly, our results are consistent with work in humans and primates. Human fMRI studies demonstrate that VTA's efferents are active when participants are making decisions related to more immediate reward (McClure et al., 2004, 2007; Tanaka

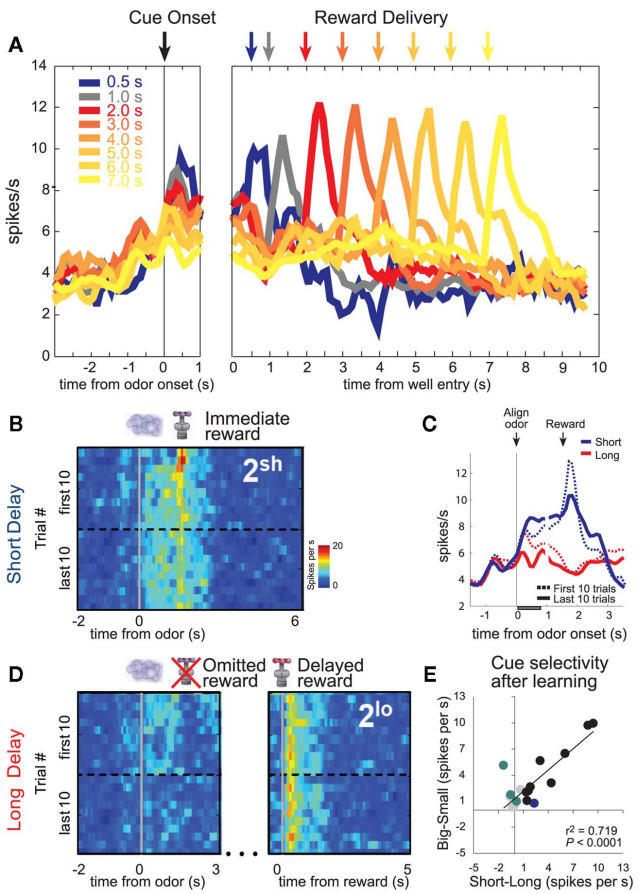

FIGURE 4 | Dopamine (DA). (A) Average firing rate of dopamine neurons over forced- and free-choice trials. Color indicates the length of the delay preceding reward delivery from 0.5 to 7 s. Activity is aligned on odor onset (left) and well entry (right). **(B,D)** Heat plots showing average activity of all cue/reward-responsive dopamine neurons during the first and last forced-choice trials in the second delay block when reward are presented earlier **(B)** or later than expected **(D)**. Activity is shown, aligned on odor onset and reward delivery. Hotter colors equal higher firing rates. **(C)** Plots the average firing over short and long delay trials aligned on odor onset. Dashed and solid lines represent activity during early and late periods of learning. Gray bar indicates analysis epoch for "E." **(E)** Cue-evoked activity in reward-responsive dopamine neurons covaries with the delay and size of the predicted reward and its relative value. Comparison of the difference in firing rate on high- versus low value trials for each cue/reward-responsive DA neuron, calculated separately for "delay" (short minus long) and "reward" blocks (big minus small). Colored dots represent those neurons that showed a significant difference in firing between "high" and "low" conditions (*t*-test; $p < 0.05$; Blue: delay; Green: reward; Black: both reward and delay). Data is taken after learning (last 15 trials; adapted from Roesch et al., 2007b).

et al., 2004; Kable and Glimcher, 2007; Ballard and Knutson, 2009). Direct recordings from primate DA neurons during performance of a simple pavlovian task are also consistent with our results (Fiorillo et al., 2008; Kobayashi and Schultz, 2008). As in our study, activity during delivery of delayed reward was positively correlated with the delay preceding it reflecting the uncertainty or unpredictability of the delayed reward. This might reflect the possibility that longer delays are harder to time (Church and Gibbon, 1982; Kobayashi and Schultz, 2008). Consistent with this interpretation, monkeys could not accurately predict the delivery of the delayed reward as measured by anticipatory licking (Kobayashi and Schultz, 2008). Also consistent with our work, activity during sampling of cues that predicted reward was discounted by the expected delay. Specifically, the activity of DA neurons resembled the hyperbolic function typical of animal temporal discounting studies, reflecting stronger discounting of delayed reward when delays were relatively short.

Thus, across species, it is clear that signals related to prediction errors are modulated by cues that predict delayed reward. Such modulation must act on downstream neurons in cortex and basal ganglia to promote and suppress behavior during inter-temporal choice. Prominent in the current literature is the idea that DA transmission ultimately impacts behavioral output by influencing basal ganglia output structures such as SNr via modulation of D1 and D2 type receptors in dorsal striatum (DS; Bromberg-Martin et al., 2010; Hong and Hikosaka, 2011). Indeed, we and others have recently shown that DS and SNr neurons incorporate anticipated delay into their response selective firing during and prior to the decision to move (Stalnaker et al., 2010; Bryden et al., 2011; Cai et al., 2011).

We propose that bursting of DA neurons to rewards that are delivered earlier than expected and the cues that come to predict them would activate the D1 mediated direct pathway, directing behavior toward the more immediate reward (Bromberg-Martin et al., 2010). Low levels of dopamine, as observed when rewards are unexpectedly delayed would activate the D2 mediated indirect pathway so that movement toward the well that elicited the delayed reward would be suppressed (Frank, 2005; Bromberg-Martin et al., 2010). Consistent with this hypothesis, it has been shown that high and low DA receptor activation promotes potentiation of the direct and indirect pathway, respectively (Shen et al., 2008), and that striatal D1 receptor blockade selectively impairs movements to rewarded targets, whereas D2 receptor blockade selectively suppresses movements to non-rewarded locations (Nakamura and Hikosaka, 2006).

VENTRAL STRIATUM

Post-training lesions of VS, in particular nucleus accumbens core, induces impulsive choice of small-immediate reward over large-delayed reward (Cousins et al., 1996; Cardinal et al., 2001, 2004; Bezzina et al., 2007; Floresco et al., 2008; Kalenscher and Pennartz, 2008). Although there are several theories about the function of VS, one prominent theory suggests that VS serves as a limbic-motor interface, integrating value information with motor output (Mogenson et al., 1980). Consistent with this notion, several labs have shown that VS incorporates expected value information into its neural firing (Bowman et al., 1996; Hassani et al., 2001; Carelli, 2002; Cromwell and Schultz, 2003; Setlow et al., 2003; Janak et al., 2004; Tanaka et al., 2004; Nicola, 2007; Khamassi et al., 2008; Ito and Doya, 2009; van der Meer and Redish, 2009). Until recently, it was unknown whether VS incorporated expected delay information into this value calculation, possibly serving as a potential source by which representations of delayed reward might impact inter-temporal choice.

We have recently shown that single neurons in VS signal the value of the chosen action during performance of our choice task (Roesch et al., 2009). The majority of cue-responsive neurons in VS fired significantly more strongly when rats anticipated high value reward in one of the two movement directions. This is illustrated in **Figures 5A–D**, which plots the average firing rate of all cue-responsive neurons in VS for responses made in each cell's preferred and non-preferred movement fields. Activity was stronger prior to a response in the cell's preferred direction (left column) when the expected outcome was either a short delay (**Figure 5A**; black) or a large reward (**Figure 5C**; black) compared to a long delay (**Figure 5A**; gray) or a small reward (**Figure 5C**; gray), respectively. This activity most likely reflects common changes in motivation because neural firing during this period was correlated with the motivational level of the rat, which was high under short delay and large reward conditions (**Figure 5E,F**; Roesch et al., 2009). This result is consistent with previous work showing that activity in VS is modulated during inter-temporal choice for immediate rewards (McClure et al., 2004, 2007; Kable and Glimcher, 2007; Ballard and Knutson, 2009) suggesting that VS is involved in decisions regarding discounted reward (but see Day et al., 2011). We suspect that increased activation of neurons that signal movement during short delay trials might cause animals to choose the more immediate reward over the delayed reward through some sort of winner take all mechanism (Pennartz et al., 1994; Redgrave et al., 1999; Nicola, 2007; Taha et al., 2007).

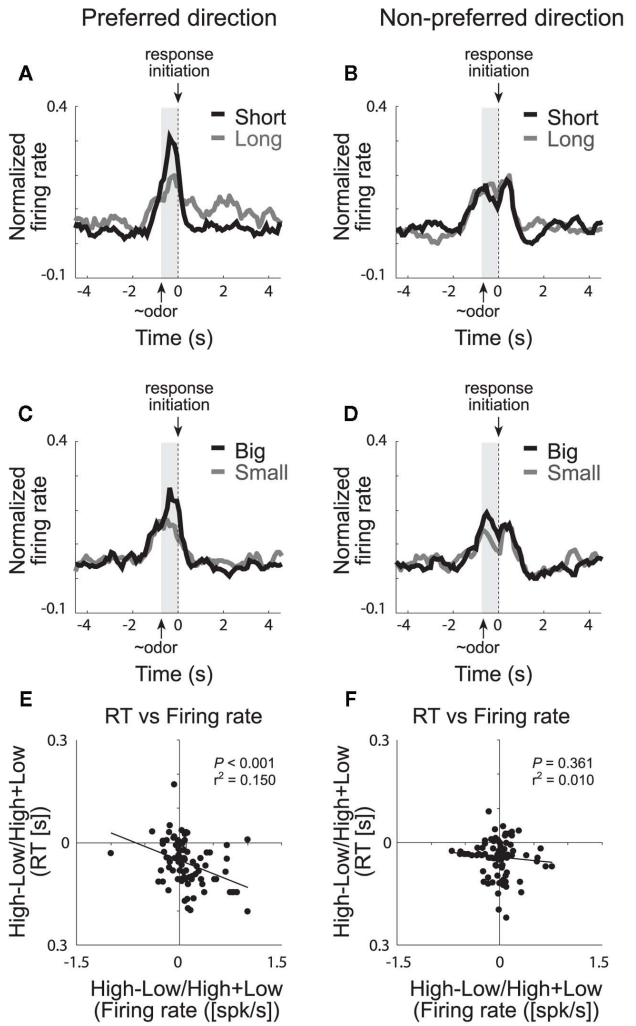

FIGURE 5 | Ventral striatum (VS). Population activity of odor-responsive neurons reflected motivational value and response direction on forced-choice trials. **(A–D)** Curves representing normalized population firing rate during performance of forced-choice trials for the odor-responsive neurons as a function of time under the eight task conditions (high value = black; low value = gray). Data are aligned on odor port exit. Preferred and non-preferred directions are represented in left and right columns, respectively. For each neuron, the direction that yielded the maximal response was designated as preferred. Correlations in the preferred **(E)** and non-preferred **(F)** direction between value indices (short − long/short + long and big − small/big + small) computed for firing rate (during odor sampling) and reaction time (speed at which rats exited the odor port after sampling the odor; adapted from Roesch et al., 2009).

Several studies, including ours, have also shown that VS neurons fire in anticipation of the reward (Roesch et al., 2009). This is apparent in **Figure 5A**, which illustrates that activity was higher after the response in the cell's preferred direction on long delay (gray) compared to short delay trials (black). Interestingly, the difference in firing between short and long delay trials after the behavioral response was also correlated with reaction time, however the direction of this correlation was the opposite of that prior to the movement. That is, slower responding on long delay trials, after the choice, resulted in stronger firing rates during the delay preceding reward delivery. If activity in VS during decision-making

Others suggest that temporally discounted value signals in VS have less to do with the actual choice – which appears to be more reliably encoded in DS – and more to do with encoding the sum of the temporally discounted values of the available options, that is, the overall goodness of the situation. Unlike our task, monkeys, on each trial, were presented with two options simultaneously. Each option varied in magnitude and delay, and the location of the better reward varied randomly. Color and number of cues signaled size and delay, respectively. These contingencies did not change over the course of the experiment.

Not only was activity in VS modulated by the value of the delayed reward in this study, neurons in VS were more likely to encode the sum of the temporally discounted value of the two targets than the differences between them or the choice that the monkey was about to make (Cai et al., 2011). Our results are similar to these in that activity in VS was modulated by size and delay, however we clearly show that activity in VS signaled the value and the direction of the chosen option. This difference likely reflects differences in the task design. In our task, rats form response biases to one direction over the other during the course of the block and rats constantly had to modify their behavior when contingencies changed, thus response–outcome contingencies were very important in our task. Further, we could not access whether or not activity in VS represented the overall value of the two options because the overall value of the reward did not change from block to block. This was an important and interesting feature of the monkey task and it is highly likely that monkeys paid close attention to the overall value associated with each trial before deciding which option to ultimately choose.

reflects motivation, as we have suggested, then activity during this period may reflect the exertion of increased will to remain in the well to receive reward. As described above for OFC and ABL, this expectancy signal might be critical for maintaining responding when rewards become delayed. Loss of this signal would reduce the rat's capacity to maintain motivation during reward delays as described in other contexts (Cousins et al., 1996; Cardinal et al., 2001, 2004; Bezzina et al., 2007; Floresco et al., 2008; Kalenscher and Pennartz, 2008).

Our data suggest two conflicting roles for VS in delay discounting. We speculate that different training procedures might change the relative contributions of these two functions. For example, if animals were highly trained to reverse behaviors based on discounted reward, as in the recording setting used here, they might be less reliant on VS to maintain the value of the discounted reward. In this situation, the primary effect of VS manipulations might be to reduce impulsive choice of the more immediate reward. On the other hand, maintaining reward information across the delay might be more critical early on during learning, when rats are learning contingencies between responses and their outcomes. Increasing delays between the instrumental response and reinforcer impairs learning in normal animals and is exacerbated after VS lesions (Cardinal et al., 2004).

Besides directly driving behavior, as proposed above, other theories suggest that VS might also be involved in providing expectancy information to downstream areas as part of the "Critic" in the actor–critic model (Joel et al., 2002; O'Doherty et al., 2004). In this model the Critic stores and learns values of states which in turn are used to compute prediction errors necessary for learning and adaptive behavior. Neural instantiations of this model suggests that it is VS that signals the predicted value of the upcoming decision, which in turn impacts prediction error encoding by dopamine neurons. Subsequently, DA prediction errors modify behavior via connections with the DS (Actor) and update predicted value signals in VS. Thus, signaling of immediate and delayed reward by VS would have a profound impact on reinforcement learning in this circuit as we will discuss below.

INTEGRATION OF SIZE AND DELAY ENCODING

Do brain areas integrate size and delay information, providing a context-free representation of value (Montague and Berns, 2002; Kringelbach, 2005; Padoa-Schioppa, 2011)? If this hypothesis is so, then neural activity that encodes the delay to reward should also be influenced by changes in reward magnitude, either at a single-unit or population level. We found that when delay and reward size were manipulated across different blocks of trials, OFC, ABL, and DS maintained dissociable representations of the value of differently delayed and sized rewards. Even in VS, where the population neurons fired more strongly to short delay and large reward conditions and activity was correlated with motivational strength, there was only a slight insignificant tendency for single neurons to represent both size and delay components. Although many neurons did encode reward size and delay length at the single cell level, many neurons encoded one but not the other. This apparent trend toward common encoding likely reflects the integration of value into motor signals at the level of VS which is further downstream than areas such as OFC and ABL.

Consistent with this hypothesis, when we recorded from neurons more closely tied to the output of the basal ganglia, we found that activity in SNr showed a significant positive correlation between reward size and delay (Bryden et al., 2011). This is illustrated in the single cell example in **Figure 6A**. Activity was higher for short delay and large reward conditions for movements made into the right well. Unlike OFC, ABL, and VS, those SNr neurons that fired more strongly for cues that predicted short delay (over long delay) significantly tended to fire more strongly for cues that predicted the large reward (over small reward; **Figure 6B**) similar to what we described for DA neurons in VTA (**Figure 4E**).

Although these results are consistent with the notion that activity in SNr reflects a common output, even in SNr, correlations between delay and size were relatively weak; leaving open the interpretation that SNr might also maintain independent representations of expected size and delay. These data suggest that we have to move very close to the motor system before delay and size are represented as a common signal, and it is not clear whether such representations exist in many regions upstream. According to our data, the majority of brain areas involved in the circuit critical for learning and decision-making based on expected outcomes and violations of those expectations encode delayed reward independently from reward size.

The fact that we were able to dissociate the effects of reward size and delay on single-unit activity in these areas indicates that encoding of discounted reward might involve different neural processes than those that signal expected reward value. This dissociation is perhaps not surprising considering recent behavioral data that supports the view that learning about sensory and temporal features of stimuli involve different underlying systems (Delamater and Oakeshott, 2007) and that studies that report abnormal delay discounting functions often report no observable change in behaviors guided by reward size.

With that said, other studies have shown that neural activity related to size and delay are correlated in several frontal areas in primate cortex (Roesch and Olson, 2005a,b; Kim et al., 2008). For example, in primates, OFC neurons that fired more strongly for shorter delays tended to fire more strongly for larger rewards. Our ability to detect independent encoding might reflect a species difference and/or a number of other task parameters; however we would like to think that differences might emerge from different levels of training. With extended training, OFC neurons may become optimized to provide generic value representations. This would have interesting implications as it would suggest that OFC and possibly other brain areas might refrain from putting delay and size on a common value scale until they have been integrated for an extended time. This might be why single neurons in primate frontal cortex and striatum have been shown to be modulated by both size and delay (Kim et al., 2008; Cai et al., 2011).

Another possibility is that common value signals observed in primates reflect the fact that, over time, short delay trials sometimes led to more reward. That is, since short delay trials took less time to complete, more reward could be obtained over the course of the recording session. Unlike the rat work, delays were not normalized in some of these studies (Roesch and Olson, 2005a,b), thus raising the possibility that brain areas might commonly encode size and delay only when shorter delays are genuinely more valuable,

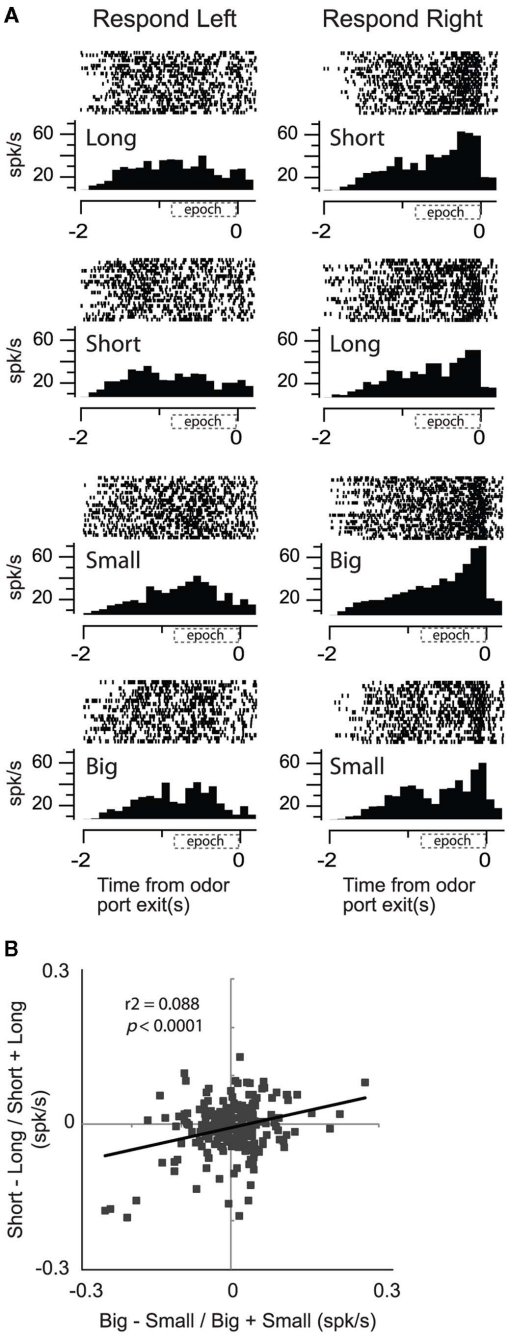

FIGURE 6 | Substantial nigra pars reticulata (SNr). Activity of single neurons in SNr reflects an interaction between expected value and direction. **(A)** Activity of a single SNr neuron averaged over all trials for each condition aligned on odor port exit during all eight conditions (four rewards × two directions). Histogram represents average activity over the last 10 trials (after learning) for each condition in a block of trials. Each tick mark is an action potential and trials are represented by rows. All trials are shown. **(B)** Correlation between size (big − small/big + small) and delay (short − long/short + long) effects averaged across direction (odor onset to odor port exit). Data was taken after learning (last 10 trials for each condition within each block; Bryden et al., 2011).

not just subjectively preferred. The possibility that these variables might be encoded separately in primates is also consistent with recent work showing that risk is sometimes encoded separately from reward size in primate OFC (Kennerley and Wallis, 2009; Kennerley et al., 2009, O'Neill and Schultz, 2010; Schultz, 2010; Wallis and Kennerley, 2010).

A final possibility is that we did not vary delay and magnitude simultaneously. True discounting studies manipulate size and delay at the same time to demonstrate the antagonistic effects of reward magnitude and delay. Certainly, Lee and colleagues have found more integrative encoding of value in the brain than we have using this procedure (Kim et al., 2008; Cai et al., 2011). This would suggest that when size and delay are manipulated simultaneously the brain encodes them together, but when they are split apart, they are represented independently. More work is necessary to determine if this theory holds up. Still, there are other differences between tasks that might impact how the brain encodes these two variables. In our task rats are constantly forming and updating response–outcome associations as they learn to bias behavior in one direction when rewards change in size or delay. Independent representations of size and delay might help the brain cope with these changing circumstances.

That fact that size and delay are not strongly correlated in most brain areas that we have tested does not mean that the rat or that other brain areas might treat them similarly. Remarkably, out of all the brain areas that we have recorded from in this task only the firing of DA neurons in VTA showed a strong clear cut relationship between manipulations of delay and size (**Figure 4E**). DA neurons fired more strongly to cues that predicted a short delay and large reward and were inhibited by cues that predicted a small reward and a long delay (**Figure 4E**). These were the same neurons in which activity reflected prediction errors during unexpected reward delivery and omission when reward was made larger or smaller than expected and when reward was delivered earlier or later than expected (**Figure 4**). The fact that the activity of DA neurons represents cues that predict expected size and delay similarly does not fit well with the finding that other areas do not, considering that it is dopaminergic input that is thought to train up associations in these areas. Why and how delay information remains represented separately from value is an intriguing question and requires further investigation.

CONCLUSION

Here we speculate on the circuit that drives discounting behavior based on the neural correlates related to size and delay as described above. It is important to remember that much of this is based on neural correlates and we are currently trying to work out the circuit using lesion and inactivation techniques combined with single-unit recordings.

According to our data, when an immediate reward is delivered unexpectedly, DA neurons burst, consistent with a signal that detects errors in reward prediction (Roesch et al., 2007b). ABL neurons also respond to unexpected immediate reward but several trials later, consistent with signals that detect the need for increased attention or event processing during learning (Roesch et al., 2010b). As the rat learns to anticipate the reward, expectancy

signals in OFC, ABL, and VS develop. We suspect that development of expectancy signals first occurs in OFC as a consequence of error detection by DA neurons, and that OFC is critical for the development of expectancy signals in ABL and VS. Although all three areas fire in anticipation of reward, they might be carrying unique signals related to reward outcome values, attention, and motivation, respectively. As expectancy signals increase, prediction error signaling at the time of reward delivery decrease and firing of DA neurons start to fire to cues that predict the immediate reward (**Figure 4**). Cue-evoked responses that develop in DA neurons subsequently stamp in associations in OFC, VS, and DS. Interactions between ABL and these areas might be particularly important in this process; lesions of ABL impairs cue development in OFC and VS (Schoenbaum et al., 2003; Schoenbaum and Roesch, 2005; Ambroggi et al., 2008). It is still unclear whether ABL–DA interactions are necessary for cue selectivity to develop in themselves and in downstream areas (Roesch et al., 2010a). After learning, OFC and VS guide decision-making via reward specific outcome values and affective/motivational associations, respectively and with DS guiding behavior by signaling action–value and stimulus–response associations (Stalnaker et al., 2010). Positive prediction errors likely impact striatal output via D1 mediated direct pathways to SNr promoting movement via disinhibition of downstream motor areas (Bromberg-Martin et al., 2010).

So what happens when rewards are delayed? After learning, there are strong expectancy signals in OFC for the immediate reward. Expectancy activity in OFC for the immediate reward persists even when reward is no longer available at that time (e.g., **Figure 2B**). Thus, when the immediate reward is not delivered, a strong negative prediction error is generated by DA neurons (**Figure 4B**). Inhibition of DA should reduce associability with reward in downstream areas, thus inhibiting responses to cues signaling the location of the delayed reward. Further, attenuated expectancy signals generated in OFC would reduce expectancy signals reliant on it, as shown for ABL and possibly for VS, that might aid in maintaining responding for the now delayed reward (Saddoris et al., 2005). Reduction of these signals might further decrease associability with the delayed reward. Subsequently, DA neurons start to inhibit firing to cues that predict the delayed reward, weakening associations in downstream areas such as OFC, ABL, and striatum. Decreased DA transmission in striatum would impact the D2 mediated indirect pathway inducing increases in SNr firing that increases suppression of movement by inhibiting downstream motor structures (Bromberg-Martin et al., 2010).

It is important to note that these are not the only brain areas involved in temporal discounting and inter-temporal choice. Serotonin clearly plays a role but exactly what role it plays is still a little murky. Serotonin depletion, sometimes, but not always, steepens the discounting of delayed rewards making animals more impulsive (Wogar et al., 1993; Harrison et al., 1997; Bizot et al., 1999; Evenden and Ryan, 1999; Mobini et al., 2000a,b; Cardinal et al., 2004; Winstanley et al., 2004a,c; Denk et al., 2005; Cardinal, 2006), and increased extracellular serotonin concentrations promotes selection of large-delayed reward over smaller immediate reward (Bizot et al., 1988, 1999). Furthermore, recent data demonstrates that serotonin efflux in rat dorsal raphe nucleus increase when animals have to wait for reward and single dorsal raphe neurons fire in anticipation of delayed reward (Miyazaki et al., 2011a,b).

Work in humans has also clearly defined a role for PFC and other cortical areas in inter-temporal choice especially when decisions have to made for rewards that will arrive in the distant future (e.g., months to years; McClure et al., 2004, 2007; Tanaka et al., 2004; Kable and Glimcher, 2007; Ballard and Knutson, 2009; Figner et al., 2010). These systems likely interact on several levels to control behavior when expected rewards are delayed.

In conclusion, it is clear that discounting behavior is complicated and impacts a number of systems. From the results described above, when an individual chooses between an immediate versus delayed reward, the decision ultimately depends on previous experience with the delayed reward and the impact that a delayed reward has on neural processes related to reward expectation, prediction error encoding, attention, motivation, and the development of associations between stimuli, responses, and outcome values. To elucidate the underlying cause of the many disorders that impact impulsivity, we must address which of these processes are impaired and further test the circuit involved in inter-temporal choice.

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