Hormonal and Genetic Influences on Processing Reward and Social Information

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ABSTRACT: Social neuroscience is an emerging interdisciplinary field that combines tools from cognitive, cellular, and molecular neuroscience to understand the neural mechanisms underlying human interactions, emphasizing the complementary nature of different organization levels in the social and biological domains. Previous studies focused on the molecular/neuronal substrates of a variety of complex behaviors, such as parental behavior and pair bonding. Less is known about the various factors influencing interindividual differences in reward processing and decision making in social contexts, both relying upon the dopaminergic system. This review concerns (1) basic electrophysiological findings and recent neuroimaging findings showing that reward processing and social interaction processes share common neural substrates and (2) genetic and hormonal influences on these processes. Recent research combining molecular genetics, endocrinology, and neuroimaging demonstrated that variations in dopamine-related genes and in hormone levels affect the physiological properties of the dopaminergic system in nonhuman primates and modulate the processing of reward and social information in humans. These findings are important because they indicate the neural influence of genes conferring vulnerability to develop neuropathologies such as drug addiction and pathological gambling. Taken together, the reviewed data start to unveil the relationships between genes, hormones, and the functioning of the reward system, as well as decision making in social contexts, and provide a link between molecular, cellular, and social cognitive levels in humans.

KEYWORDS: fMRI; reward system; dopamine; social interaction; genes; COMT; DAT; gonadal steroid hormones; estrogen; progesterone; oxytocin; reward uncertainty; neuroeconomy; cooperation; competition; fairness; trust; social exclusion

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By using classical methods from cognitive neuroscience (e.g., neuropsychology and neuroimaging), as well as molecular and cellular methods, social neuroscience focuses on how the human brain processes social information. Social neuroscience emphasizes the complementary nature of different levels of organization in the social (e.g., relational, collective, societal) and biological (e.g., molecular, cellular, system) domains and investigates how multilevel analyses can foster understanding of the mechanisms underlying human social interactions. Recent studies have tackled problems such as the molecular/neuronal substrates of a variety of complex behaviors, such as parental behavior, pair bonding, monogamy, and the neural changes associated with social experience and social interactions (e.g., evaluation of social status, trust, cooperation, exclusion).[1]

Reward prediction and evaluation are crucial functions for survival in a variable environment and are fundamental for complex behavior such as learning and motivation. The reward system, composed mainly of dopaminergic neurons and their projection sites (structures that include the ventral striatum, the anterior cingulate cortex [ACC], and the orbitofrontal cortex [OFC]), is crucial to represent and detect various types of rewards.[2] Dysfunction of this brain network seriously impairs reward processing, motivation, and decision making, as observed in many neurological and psychiatric disorders (pathological gambling, drug addiction, schizophrenia, Parkinson's disease). Currently, basic electrophysiological properties of the reward system are more fully understood during simple paradigms associating cues and rewards (e.g., classical conditioning) than during complex adaptive behavior requiring choices in social contexts. However, recent functional magnetic resonance imaging (fMRI) studies have started to investigate the neurobiological substrates of more complex reward processing, as well as of social cognition at the system level.[3–5]

Advances in molecular genetics, endocrinology, and neuroimaging start to unravel the relationships between genes, hormonal status, cognition, and functional brain regions and to build new bridges between molecular, cellular, and social cognitive neuroscience systems levels in humans. This approach is fruitful for understanding the genetic/hormonal influences contributing to individual differences in normal and pathological conditions involving dysfunctions of the reward system and of social behavior (e.g., neurodevelopmental disorders, such as autism and schizophrenia, and genetic disorders, such as Williams syndrome).[6–8]

There are important interindividual differences concerning reward processing and decision making.[9] It has been hypothesized that genetic variability in dopaminergic function could be related to these differences. However, exactly how variations of dopamine-related genes influence the reward system remain poorly understood. A major question is therefore to identify genetic polymorphisms influencing dopamine transmission and to investigate how individual differences in dopamine transmission affect the response of the reward system. Elucidating this question should help to clarify biological mechanisms

underlying individual differences in reward processing, as well as normal variability and risk for pathological disorders involving the dopaminergic system. To bridge the gap between genetics and behavior, recent studies combined genetics and personality assessment with brain imaging as an intermediate endophenotype, an approach based on the assumption that brain activation is causally more directly linked to genotype than is behavior.[10]

Similarly, there is a within-subject variability in mood and cognitive functions according to variations in hormone levels. How gonadal steroid hormones and neuropeptides regulate brain physiology is helpful not only to understand sex-specific behaviors in health and disease but also to clarify how brain activity changes with these factors during social interactions and processing of reward information. For example, during the menstrual cycle, plasma concentrations of gonadal steroid hormones such as estradiol and progesterone vary systematically, which is associated with cyclic modulations of mood and cognitive abilities,[11,12] and have been shown to modulate the activity of the reward system.[13]

In this article, we will first focus on basic processing of reward information in nonhuman primates and in humans. Second, we will review recent fMRI evidence in humans showing that processes involved in social interaction share common neural substrates with basic reward processing. Finally, we will review the recent literature on hormonal and genetic influences on reward and social interaction functions, illustrating the current integration between molecular, cellular, and brain imaging levels.

BASIC PROCESSING OF REWARD INFORMATION

Seeking rewards and avoiding punishments is a common behavior of animals, including humans. This behavior is based on the capacity to represent the value of rewarding and punishing stimuli, which is essential to predict when they might occur, and to use these predictions to make decisions prospectively.[14] Rewards are those stimuli that increase the frequency of behavior leading to their acquisition.[2] Three functions of reward have been proposed[15]: they induce learning (positive reinforcement), they induce approach and consummatory behavior for acquiring the reward object, and they induce positive emotions.[15] Rewards can serve as goals of behavior if the reward and the contingency between action and reward are represented in the brain during the action. By contrast, punishments induce avoidance and withdrawal behaviors, as well as negative emotions. Although animal studies commonly use juice as the (primary) reward, most human neuroimaging studies have used monetary (secondary) reward. Several factors may explain why money has been widely used for the study of the reward system in humans. First, it is motivationally salient and valued for most people. Second, it is scalable, allowing comparison across different amounts. Third, it is reversible, allowing comparison between rewarding (i.e., gain) and aversive (i.e., loss) circumstances.[16]

Electrophysiological Studies on Dopaminergic Neurons in Monkeys

Neurons that respond to rewards and reward-predicting stimuli have been identified in a number of brain structures receiving projections from midbrain dopaminergic neurons, such as the ventral striatum, the dorsolateral prefrontal cortex (DLPFC) and orbital prefrontal cortex, the ACC, and the amygdala.[2] The integrity of midbrain dopaminergic neurons is particularly important for the efficient functioning of this system. Electrophysiological studies in monkeys indicate that midbrain dopaminergic neurons exhibit two modes of firing: a phasic signal that varies linearly with reward probability and a sustained signal that varies highly nonlinearly with reward probability and that is highest with maximal reward uncertainty (reward probability = 0.5).[17]

It has been proposed that the phasic mode of dopamine neuronal activity codes a reward prediction error, that is, a discrepancy between the reward obtained and the reward that was predicted to occur.[2,18] Indeed, after learning, if a reward is not present at the expected time of delivery, or if it is lower than expected, the firing of dopamine neurons is depressed below their basal rates. In contrast, unexpected rewards or rewards higher than expected produce a phasic increase in the firing rate of the dopamine neurons at the time of their delivery. Moreover, after repeated pairings of a cue followed by a reward, the phasic activity of dopaminergic neurons shifts from the time of the reward delivery to the cue onset. This phasic dopamine signal may be used as a teaching signal by other structures to learn reward-directed behavior, through the repeated comparison between the expected and the actual outcomes. Moreover, at the time of the conditioned stimulus, this phasic activity increases with the expected value (product of reward probability and magnitude).[17,19]

In addition to their phasic activity, dopamine neurons also exhibit a sustained mode of activity after learning that is maximal with highest reward uncertainty (i. e., $P = 0.5$). This activity grows from the onset of the conditioned stimulus to the time of the reward delivery.[17] This sustained mode of activity occurring with maximal reward uncertainty may be related to a specific form of attention,[20] to motivational processes in the context of reward uncertainty, or to the expectation of reward information following rules from information theory.[21] According to this theory, the more uncertain the outcome (reward or no reward), the more information it conveys. Thus, monkey electrophysiological studies have shown that two different modes of dopaminergic activity may code apparently distinct statistical parameters of reward information: a phasic mode of activity coding a reward prediction error and a sustained mode of activity reflecting reward uncertainty.

fMRI Studies on Reward Prediction Error and Reward Uncertainty

A number of fMRI studies have investigated the neural correlates of the reward prediction error signal. The administration of juice and water in an

unpredicted manner was found to elicit greater blood oxygen level-dependent (BOLD) changes in the ventral striatum than administration in a predicted fashion.[22] Also consistent with this reward prediction error theory, the BOLD signal in the ventral striatum has been found to change through the course of conditioning experiments.[23–25] Before training, the delivery of a reward generates a positive prediction error response. With training, this prediction error shifts to the time of the conditioned stimulus, and this prediction error signal is reflected in striatal activity.[24,25] Furthermore, the omission of a reward at its predicted time of delivery generates a negative prediction error. The ventral striatum has also been found to be activated when distinguishing the anticipatory period before the potential reward[26] from the outcome phase at the time of reward delivery.[27] In addition to the ventral striatum, some fMRI studies also reported that the DLPFC, inferior frontal gyrus and OFC correlate with the prediction error signal, either related to abstract stimulus-response associations or to taste reward.[22,24,28–30]

A recent functional neuroimaging study extends the notions of learning signals by assessing the neural substrates of a fictive error signal.[3] This signal encodes ongoing differences between experienced returns and returns that could have been experienced if decisions had been different, that is, a learning signal associated with the actions not taken. The authors used a sequential investment task in which after each decision, information was revealed regarding whether higher or lower investments would have been a better choice. The natural learning signal for criticizing each choice was the difference between the best return that could have been obtained and the actual gain or loss, that is, the fictive error. Behaviorally, the fictive error was found to be an important determinant of the next investment. The analysis of the fMRI data revealed that the fictive error signal produced a response in the ventral caudate that was not explained by the temporal difference error signal. Taking into account the fictive error signals into learning models may provide additional insight into both normal and altered decision making.

Until recently, although a number of studies have investigated the neural correlates of the prediction error, it was still unclear whether distinct brain networks code separately the prediction error and reward uncertainty signals. To answer this question, we have used fMRI to distinguish the phasic and sustained modes of reward activity in humans.[31] Using an event-related fMRI paradigm that systematically varied monetary reward probability, magnitude and expected reward value, we found that the dopaminergic midbrain responded transiently both to higher reward probability at the cue and to lower reward probability at the rewarded outcome, and in a sustained manner to reward uncertainty during the delay period (FIG. 1). These results support the view that midbrain dopaminergic neurons follow the same basic principles of neuronal computation in humans and monkeys.

Furthermore, we observed distinct activity dynamics in target regions of the dopaminergic neurons, the prefrontal cortex responding to the transient

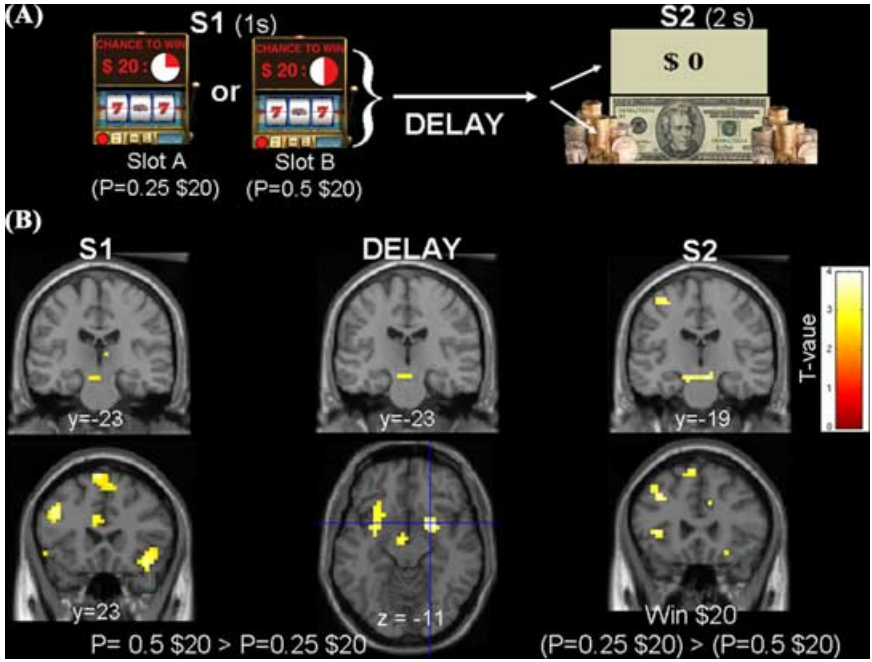

FIGURE 1. (**A**). Task design. Four types of "slot machines" were presented pseudo-randomly on a screen. The probabilities of winning different amounts of money or nothing were indicated, respectively, by the red and white portions of a pie chart above the slot machines. Each trial consisted of a brief (1 s) presentation of the cue (stimulus S1, one of the four slot machines), followed after a fixed delay (14 s) by the outcome S2 (either $0 or a picture of a $10 or $20 bill, lasting 2 s). (**B**). Location of transient (S1 and S2) and sustained (during delay) brain responses in humans. *Left and right*. The midbrain and a prefrontal network covaried with the prediction error signal at the cue S1 and at the time of the rewarded outcome S2. *Middle*. Location of sustained midbrain and ventral striatum activities covarying with the reward uncertainty signal ($P = 0.5$) during the delay period. Consistent with electrophysiological recordings, the human midbrain region was transiently activated with higher reward probability at the cue S1, with lower reward probability at the rewarded outcome S2 and showed higher sustained activity with reward uncertainty during the delay period. Reprinted and modified with permission from REF.[31] © (2006) Oxford University Press.

prediction error signal, and the ventral striatum covarying with the sustained reward uncertainty signal. Our findings may indicate that dopaminergic projection sites can distinguish the two signals.[31] These targets may also show independent transient (prefrontal cortex) and sustained (ventral striatum) activities and/or may help to shape differentially the phasic and sustained modes of midbrain firing. Because the development of the mesolimbic/nigrostriatal dopaminergic pathways occurred earlier than the mesocortical pathway during evolution, our findings suggest that specific functional brain networks

developed to code distinct aspects of the statistical properties of reward information.[31] The absence of activation in the ventral striatum/putamen covarying with the prediction error signal could be explained by the fact that nothing had to be learned in our task.[31]

Importantly, our monetary reward task was purposely designed to use a long delay interval (=14 s) between the cue (slot machine) and the outcome, which allowed us to disentangle the phasic signal from the sustained activity. This critical temporal dimension of our task is important to remember when considering different paradigms and also varying reward magnitude, probability, and/or uncertainty, which could not fully distinguish phasic and sustained aspects. For example, in one fMRI study, the ventral striatum was found more activated during anticipation (=2 s) of rewards of increasing magnitude but not of increasing probability,[32] while other studies reported increased ventral striatal activation with both higher reward magnitude and probability.[33–35]

Concerning reward uncertainty, stimuli associated with higher uncertainty (variance) have been reported to elicit increased activity in the lateral OFC.[35] Moreover, in a guessing card task in which subjects were presented with a cue card and had to decide whether the next card would be higher or lower, activity in anterior cingulate and orbitofrontal cortices was modulated by outcome uncertainty during the anticipatory period.[36] In a similar paradigm varying expected reward and risk simultaneously, in which subjects had to place a bet before actually seeing the first card, the ventral striatum showed both an immediate response with increasing reward probability and a delayed response related to risk (reward variance).[37] Finally, tasks using nonmonetary stimuli also reported modulation by categorization uncertainty[38] and decision uncertainty[39] in a network that included prefrontal, parietal, and insular cortices. The exact reasons for the discrepancies between these findings are certainly multiple, probably involving timing and task designs, and future studies will need to address these issues.

Predictive Value Coding in the Orbitofrontal Cortex and the Amygdala

In addition to the ventral striatum and the ventral tegmental area, involved in coding prediction error and reward uncertainty, distinct functions have been attributed to other components of the reward system. The two structures most consistently activated are the OFC and the amygdala, both responding to primary[40–42] and secondary[43–45] rewards.

For example, the OFC is involved in coding stimulus reward value and in concert with the amygdala and the ventral striatum is implicated in representing predicted future reward.[14] In monkeys, OFC neurons code the relative value, rather than the absolute value, of reward.[46] These neurons can discriminate between different rewards, reflecting animals' relative preferences among the available rewards rather than physical reward properties, suggesting that they process the motivational value of rewarding outcomes. Also, neurons in

the OFC respond to a particular taste or odor when the animal is hungry but decrease their firing rate after satiation.[47–49] Similarly, in humans, the OFC and the amygdala are less activated for devaluated than for nondevaluated cues for food after consumption of one food to satiation.[50] Similarly, the amygdala may play a complementary role in coding reward intensity. Although the amygdala has been traditionally linked to aversive stimuli, new evidence has emerged concerning the amygdala responding to both pleasant and unpleasant stimuli.[51,52] Two recent studies in the olfactory and gustatory domains dissociated responses to valence and intensity of the stimuli and reported that the amygdala responds to intensity but not to valence of the stimuli, whereas the OFC showed the opposite pattern.[53,54]

Neuroeconomic Approach: From Basic Reward Processing to Real-Life Purchasing Behavior

There has been a recent explosion in applying game theory and economic methods to understand how the brain responds to the various influences of cognitive and emotional bias on the decisions of purchasers, salesmen, savers, etc. One example is human loss aversion, which reflects that when deciding between risky options, humans are about twice as sensitive to the possibility of losing goods or money than to the possibility of winning them. Some studies suggest that the representation of losses entails emotional processes and consequently engages structures such as the amygdala or the anterior insula.[34,55–58] Consistent with this notion, Kuhnen and Knutson investigated why investors systematically deviate from rationality when making financial decisions.[56] Using event-related fMRI, they investigated whether anticipatory neural activity would predict optimal and suboptimal choices in a financial decision-making task and showed that distinct neural systems were engaged during financial decision making. Using a task that elicited a range of investment behaviors, including risk-seeking and risk-averse financial choices, they observed that activation in the nucleus accumbens preceded risky choices and risk-seeking mistakes, whereas activation of the anterior insula preceded riskless choices and risk-aversion mistakes. The authors indicate that the relative activation of each one of these systems may lead to different risk preferences underlying risk-seeking choices (e.g., gambling) and risk-averse choices (e.g., buying insurance). Moreover, during a purchase paradigm using neuroeconomic methods to separate distinct components of the purchase decision process in individual consumers, product preference activated the nucleus accumbens, whereas excessive prices activated the insula and deactivated the medial prefrontal cortex.[59] Response in these three brain regions predicted subsequent decisions to purchase. These results suggest that the brain frames preference as a potential gain and price as a potential loss, and that activation of brain structures such as the nucleus accumbens, related to anticipation of potential gains precedes purchasing decisions. From a neuromarketing perspective, these

findings have implications for the design of more effective sales strategies, on the basis that anticipatory activation of the nucleus accumbens by certain reward cues may increase the likelihood that individuals engage in risk-seeking behaviors. Moreover, diminishing the salience of payments (e.g., credit cards) or creating the illusion that products have no cost (e.g., rewarding frequent clients) may also decrease the effect of excessive prices.[56,59]

A recent fMRI study challenged the view that loss aversion engages a distinct emotion-related brain network (e.g., amygdala/insula) and identified a common brain network whose activity increases with potential gains and decreases with potential losses.[58,60] The authors assessed the brain activation related to the decision of whether to accept a gamble. They isolated a gain-responsive network consisting of brain regions previously associated with anticipation and receipt of monetary rewards, which included the dorsal and ventral striatum, the ventromedial prefrontal cortex, the anterior cingulate gyrus, the orbitofrontal gyrus, and the dopaminergic midbrain regions. Most of these areas also showed decreasing activity as the size of potential loss increased. Interestingly, in the striatum and the ventromedial prefrontal cortex, the slope of the decrease in activity for increasing losses was greater than the slope of the increase of activity for increasing gains, indicating that loss aversion behavior may be linked to the brain's greater sensitivity for losses than gains. These results agree with those of studies showing increased and decreased activity in the striatum for experienced monetary gains and losses,[27,45] and they support the notion that the same neural structures code losses and gains.

In the context of an organization, money is not the only reward possible. The intrinsic enjoyment derived by the task, social recognition, the opportunity to grow, autonomy, and even positive feedback from managers or peers are examples of rewarding aspects of a job and, as such, affect motivation, satisfaction, and behavior of the members of the organization. To design suitable reward plans that can motivate a heterogeneous group of workers, one must account for differences in the valuation of available rewards. For example, generational differences are reflected in the rewarding value of different job features, so different rewards might be necessary to attract a technology-savvy and innovative young worker or to retain an experienced veteran.[61]

Taken together, these studies provide important new insights into the functional properties of the reward system and of economic decision making in humans. They are particularly relevant for several neuropsychiatric and behavioral disorders, such as substance abuse and pathological gambling, that are associated with increased risk taking and impulsive behavior.

NEURAL BASES OF SOCIAL INTERACTION

The strong interdependence showed between humans, even with nonkin, might have been a key element of our evolutionary success. An example might

be the high levels of cooperation that humans express with each other, which are unmatched in the animal world. The study of social interaction has received much attention by social sciences and has recently been spotlighted by cognitive and neural sciences. Using neuroimaging techniques and adaptations of games used by economists to model social interactions, several studies have assessed the neural basis of different forms of social interaction such as cooperation, competition, punishment, and rejection.

Neuroimaging Studies on Cooperation and Competition

Inferring others' mental states is essential to cooperate and to compete. Mentalizing is the ability to explain and predict others' behavior by means of attributing them independent mental states, such as thoughts, beliefs, wishes, and intentions, which might be different from ours. One way of assessing the neural substrates of mentalizing involves comparing subjects while playing with a human (or believing they do so) versus playing with a computer. These studies have often reported that the medial prefrontal cortex and the ACC are crucial in the formation of others' mental states.[4,62,63]

Cooperation is pervasive in human societies. In consequence, effective social interactions must differentiate between those who do and do not reciprocate to decide whom to approach and whom to avoid. Mathematical models and computer simulations combining biological and economical methods demonstrate the evolutionary advantage of mutual cooperation.[64] Recent neuroimaging studies have explored the neural substrates of cooperation.[65–68] In one experiment,[65] subjects competed, cooperated, or played alone in a tokens game while they were scanned. Competition and cooperation toward a common goal, compared with playing alone, were found to activate a common frontoparietal network subserving executive functions, as well as the anterior insula, involved in the sense of agency and autonomic arousal. Cooperation activated the OFC, whereas competition activated inferior parietal and medial prefrontal cortices. According to the authors, activation in the OFC might be indicative of the socially rewarding properties of cooperation.

Data from other studies suggest that cooperative behavior engages several brain areas from the reward circuitry. In one study, subjects were scanned while playing the Prisoner's Dilemma game, in which two players independently choose to either cooperate with each other or not. The amount of money each one wins depends on his or her choices, so that the highest outcome is obtained if one defects and the partner collaborates, and the lowest outcome results the other way around. Mutual cooperation has been found to activate brain areas involved in reward processing, such as the nucleus accumbens, the caudate nucleus, and the ventromedial frontal/OFC.[66] Furthermore, reciprocated and unreciprocated cooperation have, respectively, been associated with positive and negative BOLD responses in the ventromedial prefrontal cortex

and ventral striatum.[67] These results might reflect the rewarding effects of arranging and/or experiencing a mutually cooperative social interaction. They also parallel single-neuron recordings showing that unexpected rewards activate midbrain dopaminergic neurons, whereas omission of an expected reward reduces the firing rates of these neurons.[18] In the Prisoner's Dilemma game, defection by the partner after having decided to cooperate might be seen as the omission of an anticipated reward, which may lead to the reduced activity or deactivation of the midbrain dopaminergic region and possibly of the targets to which they project. These effects might reflect the positive and negative prediction errors related to a reciprocated and unreciprocated cooperation, respectively, that would be used to learn whom we can trust to reciprocate favors and whom we cannot.

Singer *et al*. subtly used the Prisoner's Dilemma game to investigate the processing of relevant cues that acquired significance through learning in an interactive context.[68] Unlike in other studies, subjects were not scanned during the game proper but while making judgments based on the sex of people with whom they had previously interacted during the game. The insula, the OFC, the left amygdala, and the left putamen showed greater responses to cooperator faces relative to neutral faces. Defector faces induced increased activity in the ventromedial prefrontal cortex. Response in several brain regions related to reward processing, including OFC and ventral striatum, was higher for unconstrained cooperators than for cooperators that were forced to follow a predetermined pattern of response. The activation of several reward areas led the authors to propose that mutual cooperation inherently possesses a rewarding value.

Neuroimaging Studies on Fairness and Trust

Humans do not always behave rationally about money. Clear evidence comes from a study using the Ultimatum Game.[69] In this game, a proposer makes an offer to the responder on how a certain amount of money should be split between them, and the responder can either accept or reject the offer. If the offer is accepted, each participant gets the amount of money proposed, whereas if it is rejected, none of the players gets anything. The reasonable way to play the game is for the proposer to offer the smallest possible amount of money and for the responder to accept any proposal, no matter how small it may be, because a small amount is better than none. Behaviorally, participants accepted all offers considered fair (those splitting the amount around 50%), but the rate of rejection increased as the offers were considered less fair. Unfair offers elicited activation in the anterior insula, DLPFC, and ACC. Moreover, activation in the anterior insula was correlated with the degree of unfairness of an offer, and activity therein predicted acceptance of unfair offers. Interestingly, the insula has been related to the experience of several negative events, such as pain,[70] and to the evaluation of negative emotions like anger or disgust.[71,72] Activation of

the DLPFC was attributed to the fact that unfair offers require more cognitive demands to overcome the emotional impulse of rejecting the offer. Finally, ACC activation was interpreted as detecting the conflict arising between accepting an unfair (but economically reasonable) offer and emotionally rejecting it. Authors indicate that activation in the DLPFC and the anterior insula could be responsible for two opposite demands in the ultimatum game, namely, the cognitive goal of accumulating money and the emotional goal of resisting unfairness. This study stresses the importance of emotional states on decision making.

Many social interactions strongly depend on fairness and trust. Trust is essential for friendship, trade, and leadership, and plays an important role in economic exchange and politics.[73,74] Many employees believe that the outcomes they receive from an organization should be linked to the contributions they make to the organization. The reciprocation of trust in an organizational context could be exemplified by the fact that members will work harder and exhibit higher commitment if they consider that they are fairly treated. The perception of members and employees of being treated fairly has been related to many important outcomes, including employee satisfaction, commitment to the organization, trust in one's leader, and task performance, and it has been considered an important mediator of the positive effects of reward on motivations, perceptions, attitudes, and behavior of the members.[75] Unfair behaviors by leaders and managers (e.g., to show who the boss is and assert their authority) may lead to nonreciprocation by the members of the organization, culminating in demonstrations and strikes when conflicts cannot be solved more easily.

Not only do we punish unfair treatment, even when doing so is costly, but we may also obtain satisfaction from it. Altruistic punishment—the predisposition to punish social norms violators even when this imposes a cost on the punisher—is basic for the evolution and maintenance of social cooperation.[76–78] The dorsal striatum activates when subjects administer monetary punishments to defectors.[5] Moreover, activation of this region during costless punishment predicted the cost that punishers were willing to assume to punish defectors. The more the activation, the more the cost assumed. The authors conclude that caudate activation reflects the expected satisfaction from punishing. A later study reported increased activation in reward-related areas when observing unfair partners receiving pain induced by a third person.[81] The brain areas reported to be activated in these studies coincide with those activated by rewarding cooperators,[66] linking two diametrically opposite behaviors by means of a common psychological experience: the anticipation of a satisfying (or rewarding) outcome.[80]

Interestingly, in an organizational context, an early study revealed that subjects reported positive affect when deserved sanctions were administered to a group member.[81] Moreover, subjects were more willing to work hard, felt more satisfied, expected higher levels of group performance, and perceived

fairer treatment from their supervisors when the supervisors punished a team member who performed poorly than when a poor-performing team member received no punishment.[81]

In most of the studies concerning social interaction, only one of the two interacting subjects was scanned. The term *hyperscanning* refers to the ability that allows the link between magnetic resonance scanners through the Internet, so that the activity of two actually interacting agents can be recorded at the same time.[82] Using hyperscanning and a multiround format of the trust game, King-Casas *et al*. assessed the neural correlates of trust. Pairs of subjects were scanned simultaneously, one of them being the investor and the other one, the trustee.[83] The investor is endowed with a certain amount of money, which he or she can invest in any portion with the trustee. The amount of money invested appreciates, so that the trustee actually receives, say, three times the amount invested. Finally, the trustee decides how much of the amount received he will repay to the investor. At the behavioral level, reciprocity by one player was the strongest predictor of subsequent increases or decreases in trust in the other player, as measured by an increased or decreased repayment in the next round. The analysis of the fMRI data revealed that activation of the trustees' caudate nuclei was higher in response to benevolent reciprocity, that is, an increase in the investment as a response to a previous defection of the trustee, compared with malevolent reciprocity, a reduction in the investment after a generous repayment by the trustee. Moreover, the activation in the caudate nucleus dynamically varied with the increases and decreases in the amount of money returned in the subsequent trial, being higher when trustees increased the repayment in the next round. The authors conclude that the activity of the trustee's caudate nucleus computes information about the fairness of a decision and the intention to repay that decision with trust. Interestingly, there was a shift in the peak of the response for the intended increases in trust. In the initial rounds this peak was observed after the investor's decision was revealed and progressively became anticipatory and occurred before the revelation of the investor's decision. These results parallel those obtained in monkey neurophysiological studies showing a shift in the phasic response of dopamine neurons through conditioning from the time of the presentation of the reward to the time of the presentation of the reward-predicting stimulus.[18] In a social interaction context, this shift might be interpreted as the development of a reputation for the partner.

Neuroimaging Studies on Social Exclusion

Given the adaptive importance of social bonds for human beings, it has been suggested that the social attachment system and the physical pain system share a common neural basis. Confirming this hypothesis, the ACC and the right ventral prefrontal cortex, both related to the affective aspects of physical pain, also respond to social pain.[84] The ACC, anterior insula, and right ventral

prefrontal cortex were activated when subjects were excluded from a ball-tossing game by the other players. Moreover, activation of the ACC and the right ventral prefrontal cortices correlated positively and negatively, respectively, with self-reported distress. Activation of these two brain areas was negatively correlated, which supports the notion that the ventral prefrontal cortex may implement a self-regulatory mechanism for mitigating the distressing effects of social exclusion. A later study found a dissociation between dorsal and ventral aspects of the ACC.[85] Subjects were scanned while viewing faces and either forming a first impression (saying whether they liked the person) or predicting whether the other person liked them. After their judgments, subjects were given feedback indicating whether the other person liked them. The fMRI data revealed that the dorsal ACC responded to expectancy violation, that is, when feedback matched versus did not match the subjects' first impressions or predictions. On the other hand, the ventral ACC responded to feedback type (positive or negative). For the authors, these data agree with a classical dissociation within the ACC, its rostral and dorsal aspects being responsible for emotional and cognitive functions, respectively.[86]

Taken together, these studies indicate a strong link between certain aspects of social interaction (e.g., cooperation) and the processing of rewards. Similarly, social exclusion could be related to aspects such as punishment or loss aversion. In fact, the ACC has been reported to be activated during experiencing both social rejection[84,85] and financial losses.[59,87] However, further studies including several aversive outcomes of different natures in the same experiment are necessary to clarify to what extent these processes share common neural substrates.

Most economic analyses are based on two major assumptions of human nature: Individuals are rational decision makers and they have purely self-regarding preferences. Altogether, behavioral and neuroimaging studies show that people often violate these assumptions,[88] especially in social settings.[89] In fact, emotions play an important role in decision making.[90,91] However, how the violation of these assumptions might affect aggregate entities, like markets and organizations, is not clear, given that there is still a share of subjects who do not violate these assumptions. This latter type of subject shapes aggregate outcomes, making them closer to those predicted by a model assuming rationality and self-regard by all the agents.[88] Furthermore, some brain regions, such as the medial prefrontal cortex and the anterior insula, may be characteristic of the interactions between human partners compared with computer partners, suggesting that decisions made during social interactions depend on something else than merely economic outcomes.[89]

HORMONAL INFLUENCES

Given the fundamental role of the dopaminergic system in reward processing and social interactions, some researchers have begun to test the hypothesis

that naturally occurring differences in dopaminergic transmission between and within subjects may affect these functions. Hormones are a source of both intraindividual and interindividual differences, some of them directly affecting the dopaminergic system.

Estrogen and Progesterone Effects on Reward Processing and Social Decision Making

Behavioral, biochemical, and physiological data in animals show that gonadal steroid hormones affect behavior and modulate neuronal activity.[92–95] Estrogen and progesterone receptors are densely expressed in structures of the dopaminergic reward system, such as the midbrain dopaminergic neurons, the ventral striatum, and the amygdala.[92] Many preclinical data, including behavioral and neurochemical differences between sexes, across the estrous cycle, and in postovariectomy hormone replacement,[96,97] demonstrate the neuroregulatory effects of estrogen and progesterone on the dopaminergic system.[98,99] These effects are not restricted to the tuberoinfundibular dopaminergic system involved in control of the anterior pituitary and important for ovulation and reproductive behavior but also to the mesocortical and mesolimbic dopaminergic systems relevant for cognition, affect, and reward processing. For instance, estrogen has a neuroprotective effect on the nigrostriatal dopaminergic system during methamphetamine-induced neurotoxicity in female rats, but not in male rats.[100] Furthermore, female rats show the highest rates of cocaine self-administration briefly after estradiol peaks, and administering estradiol to ovariectomized rats enhances cocaine self-administration.[99,101]

In women, the normal 28-day menstrual cycle is divided into two main phases. The follicular phase extends from the first day of menses until the 14th day and is characterized by low levels of progesterone and increasing levels of estradiol, which reaches a peak at ovulation. The remaining days constitute the luteal phase, characterized by high levels of progesterone and a second peak of estradiol in the midluteal phase.[102]

Hormonal changes during the menstrual cycle phases influence spatial and verbal cognitive abilities,[12,103,104] attention,[105] mood,[106] and vulnerability to drugs of abuse.[107] In a recent study, we used fMRI and an event-related monetary reward paradigm to investigate the neurophysiological effects of gonadal steroid hormones on the human reward system.[13] Women were scanned during the midfollicular and luteal phases of the menstrual cycle while performing a monetary reward task that distinguished neural concomitants of anticipating uncertain rewards from those of reward outcome. We observed that during the midfollicular phase, women showed higher activation, relative to the luteal phase, of the OFC and the amygdala during anticipation of uncertain rewards (FIG. 2). During reward delivery, we found higher activation in the midbrain, striatum, and frontopolar cortex during the follicular phase than during the luteal phase. These data support an increased reactivity of the reward system

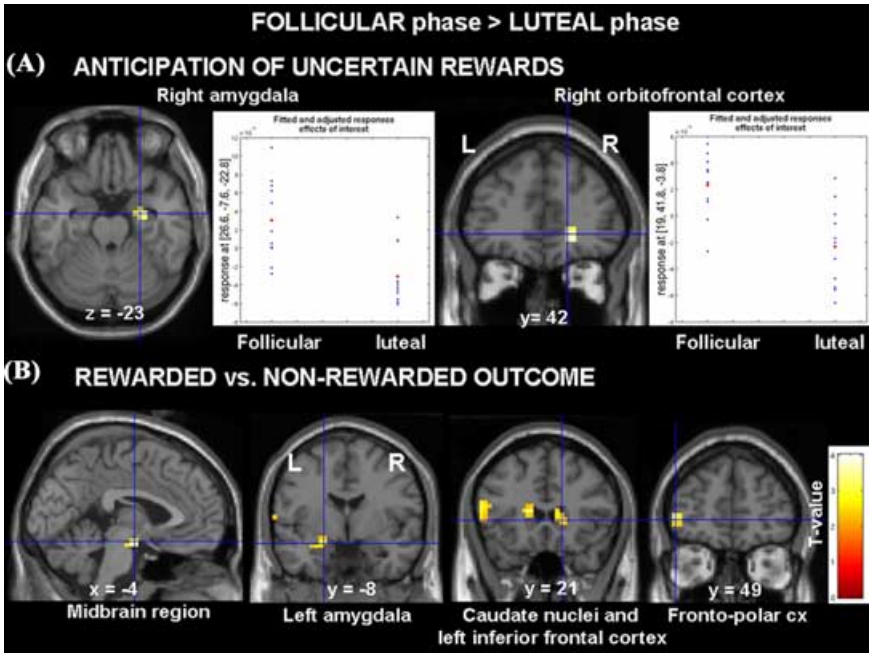

FIGURE 2. Cross–menstrual cycle phase differences in BOLD response during anticipation of uncertain rewards and at the time of the rewarded outcome. (**A**) *Left*. Statistical maps overlaid onto structural MRI showing BOLD fMRI responses greater in follicular than luteal phase during reward anticipation in the right amygdala and OFC. *Right*. Distributions of BOLD signal response for each woman. (**B**) Greater BOLD response during follicular than luteal phase at the time of the outcome in midbrain, left amygdala, heads of the caudate nuclei, left inferior frontal gyrus, and left frontopolar cortex. Reprinted and modified with permission from REF.[13] © (2007) The National Academy of Sciences.

in women during the midfollicular phase, during which estrogen is unopposed by progesterone.

Moreover, between-sex differences comparing the group of women with a group of men matched for age and level of education revealed that men activated the ventral putamen more than women during anticipation of uncertain rewards, whereas women showed stronger activation of the anterior medial prefrontal cortex during reward delivery. Finally, correlational analysis between the brain activity and the gonadal steroid levels revealed a positive correlation between activation in the amygdalo–hippocampal complex and the estradiol level, regardless of menstrual cycle phase. From an evolutionary point of view, the increased activity observed during the follicular phase may underlie the increased availability, receptivity, and desire during the ovulatory period, which has been thought to facilitate procreation.[13]

Recent neuroimaging studies have also been able to detect changes in brain activation related to menstrual cycle phase during negative emotional processing. Activity of the anterior-medial OFC for negative verbal stimuli was increased premenstrually and decreased postmenstrually, whereas the inverse pattern was observed in the lateral OFC.[108] Another study reported greater activity during the early follicular phase in response to negative, high-arousing stimuli in a set of areas involved in the response to stress, including the amygdala, the OFC, and the anterior cingulate gyrus.[109] These studies demonstrate that generally arousing stimuli may modulate similar brain networks across the menstrual cycle phases.

At the behavioral level, the effect of the menstrual cycle on social decision making was recently studied in a group of young women participating in a mock job scenario.[110] There is evidence that women's preferences for male faces shift across the menstrual cycle, with higher preference for relatively masculine traits in the follicular phase.[111–113] Participants had to assign minimum, low, high, or maximum status resources to a series of men previously rated to look either dominant (e.g., squarer jaws, smaller pupil-to-brow distance) or nondominant. A first analysis revealed that female observers assign resources of high status to dominant-looking men and resources of low status to nondominant-looking men. Further analyses showed that during the follicular phase more high-status resources were allocated to the dominant-looking men than to nondominant-looking men. Thus, women actively manipulate male status cues in a manner that is specific to the different phases of the menstrual cycle. Awareness of these and other biases, such as the influence of past and future expected interactions in reward allocation,[114] may be useful for trainings in management and human resources.

Testosterone Effects on Reward Processing and Social Behavior

In men, testosterone levels vary during the day[115,116] and with age, starting to decrease at around 40 years old.[117] Animal studies have demonstrated a relationship between testosterone and aggression.[118] In humans, a role of androgens in aggression has been inferred from studies in which samples were selected on the basis of violent behavior.[119] Although there is some evidence in favor of a positive relationship between testosterone and aggression in humans, results are not conclusive.[118–120] Dominance, that is, the enhancing of one's status over that of other people, which is often expressed nonaggressively, has also been related to higher levels of testosterone in both men and women.[121,122] Testosterone may partly explain the sex differences observed in some cognitive functions. In women, testosterone administration was found to improve spatial abilities,[123,124] putatively considered male-advantage abilities. Less is known about testosterone influences on the reward system. Testosterone levels correlated with brain activation in the OFC and the insula during processing of

visual sexual stimuli in men,[125] demonstrating that these brain areas respond to sexual arousal and not merely to a state of general motivational arousal. Activation of the OFC was interpreted as the neural correlate of an appraisal process through which visual stimuli are categorized as sexual incentives. In women, testosterone has also been reported to influence economic decision making.[126] Administering testosterone produced a more disadvantageous pattern of decision-making response in the Iowa Gambling Task, indicating reductions in punishment sensitivity and heightened reward dependency. In this task, subjects must draw a card from one of four available decks with the objective of gaining as much money as possible. Two of the decks are disadvantageous; they produce immediate large rewards, but these are accompanied by substantial money losses due to more extreme punishments. The other two decks are advantageous, because reward is modest but consistent and punishment is low. A similar study showed that low cortisol levels were related to impaired performance on this task in both men and women.[127]

Another study assessed the influence of cortisol on interpersonal trust.[128] Subjects' cortisol levels were measured before and after psychosocial stress exposure. Cortisol elevation induced by social stress was negatively correlated with the scores of General Trust Scale, suggesting that subjects with higher interpersonal trust have lower activation of the hypothalamic–pituitary–adrenal axis when exposed to social stress.

Oxytocin Effects on Social Interactions

Evidence from animal studies indicates that another class of hormone, neuropeptides oxytocin and vasopressin, play an important role in complex social behaviors, including parental care, affiliation, and pair bonding.[129,130] The study of two species of voles showing distinct reproductive strategies has provided most of the evidence. Comparative studies of prairie and montane voles, which are monogamous and polygamous, respectively,[131] have shown a different pattern of expression of oxytocin and vasopressin receptors in the brain that appears to be associated with these reproductive strategies.[129,132] Regions exhibiting such differences are the nucleus accumbens, where prairie monogamous voles have higher density of oxytocin receptors than montane voles do, and the ventral pallidal area, a major output of the nucleus accumbens, which shows higher density of vasopressin receptors in prairie voles.[130] The functional importance of these receptors is demonstrated by the fact that oxytocin agonists and antagonists specifically facilitate and block social behaviors such as pair bonding in female voles. In male voles, it is vasopressin that appears necessary for bond formation.[133,134] It has been suggested that these receptors link social information to reward circuits in the brain, providing a neurobiological mechanism for partner preference formation and social attachment.[1,130]

In humans, oxytocin has been associated with trustworthiness[137,138] and with improved ability to infer others' mental states,[137] both essential for human social interactions. In a double-blind study,[74] participants received either an intranasal dose of oxytocin or placebo before taking part in a trust game. The data showed that oxytocin increased investors' trust, as demonstrated by the larger amounts of money transferred by the investors in the oxytocin group than those in the placebo group. Moreover, this effect of oxytocin was specific to trusting behavior in social interactions, as suggested by there being no differences in the amount of money transfers between the oxytocin and the placebo groups when investors faced the same choices as in the trust game but this time with a random mechanism determining the investor's risk. Thus, the effect of oxytocin on trust is not due to a general increase in the readiness to bear risks; on the contrary, oxytocin specifically affects an individual's willingness to accept social risks arising through interpersonal interactions. The influence of oxytocin on social behavior may be mediated, at least in part, by its effects on the amygdala, which is a central component of the circuitry of fear and social cognition and shows a high expression of oxytocin receptors. Confirming this hypothesis, a recent neuroimaging study reported reduced fear-induced activation in the amygdala after administration of oxytocin.[138]

GENETIC INFLUENCES

The study of the genetic basis of human differences in complex behaviors appears as one of the most promising fields in neuroscience, favored by the advances in molecular genetics and in noninvasive functional neuroimaging techniques.[139] From the point of view of the generalist genes hypothesis, it is assumed that one gene might affect many traits and that many genes affect a trait.[140] In social organization, it has become increasingly accepted that traits, attitudes, and behaviors relevant to the workplace have a genetic component.[141] Several studies have assessed the genetic influence on some job-related variables such as leadership role occupancy,[142,143] job and occupational switching,[144] and job satisfaction.[145] These studies have been conducted on twins and have reported that around 30% of the variance observed in these variables may be explained by genetic influences.

Both reward processing and social interaction engage brain structures that lie on the ascending dopaminergic pathways. Thus, an important axis of current research is to study the brain influence of genes that affect dopaminergic transmission, to clarify the biological mechanisms underlying interindividual differences and vulnerability to pathology related to the dopaminergic system.[139,146] Behavioral and neuroimaging studies have explored the relationship between dopamine-related genes and some personality traits and behaviors related to reward, and more recently, with reward-related brain activation. These studies have focused on the genetic variations of dopamine receptors

(DRs), especially DRD2 and DRD4, and other genes coding for enzymes and transporters involved in the dopaminergic transmission, such as the catechol-*O*-methyltransferase (COMT) and the dopamine transporter (DAT).

At the behavioral level, genetic variations in DRD4 have been related to novelty seeking[147–149] and pathological gambling.[150] DRD2 has been related to drug addiction[151,152] and reward deficiency syndrome.[153,154] Neuroimaging studies have recently begun to assess the effects of dopamine-related genes on reward processing. Cohen *et al*. studied the effect of the DRD2 gene in reward processing by using an fMRI gambling task that allowed them to separate anticipation and reception of rewards.[155] Although they found no differences during reward anticipation between carriers and noncarriers of the A1 allele of the DRD2 gene, the presence of the A1 allele of the gene significantly affected neural responses at the time of the outcome. Subjects with the A1 allele showed lower response in the medial OFC, amygdala, hippocampus, and nucleus accumbens during reward outcome. This lower differentiation between receiving and not receiving rewards agrees with the idea that a reduced concentration of DRD2 receptors in the reward system reduces sensitivity to rewards. This finding may explain why individuals with the A1 allele are more likely to develop addictive or reward deficiency disorders.

Another gene implicated in the dopaminergic transmission is the COMT gene. This gene codes for the COMT enzyme, which is involved in dopamine degradation.[156–158] In humans, a functional polymorphism leads to the substitution of the amino acid valine (Val) by methionine (Met) at codon 158.[159] The enzyme containing Met is unstable at body temperatures and shows significantly lower activity than the enzyme containing Val,[160] presumably leading to higher levels of synaptic dopamine.[159,161] Although somewhat inconsistently, behavioral studies have linked the Val allele of the COMT with personality traits such as novelty-seeking[162] and risk-seeking[163] scores. Cognitively, the COMT genotype has been studied mainly on prefrontal function, the Val allele often being associated with worse performance in executive functioning.[146,164,165] This finding has received further support from our own[166] and other fMRI studies relating the number of Val alleles to lower prefrontal efficiency (higher activation for a similar level of performance) during performance of working memory tasks.[146,167] However, the effect of COMT on brain activity depends on the task at hand.[168] For instance, during the performance of emotional tasks, BOLD response in the amygdala and prefrontal connected areas correlated with the number of Met alleles during unpleasant stimuli.[169] Similarly, viewing faces expressing negative emotions elicits brain activation in the hippocampus and ventrolateral prefrontal cortex that is related in a dose-dependent fashion to the number of Met alleles.[170]

Another gene involved in dopamine transmission is the gene coding for the DAT, which terminates dopamine transmission by reuptaking released dopamine back into the presynaptic neuron. The DAT gene displays a 40-base-pair variable number of tandem repeats, with 9 and 10 repeats being the

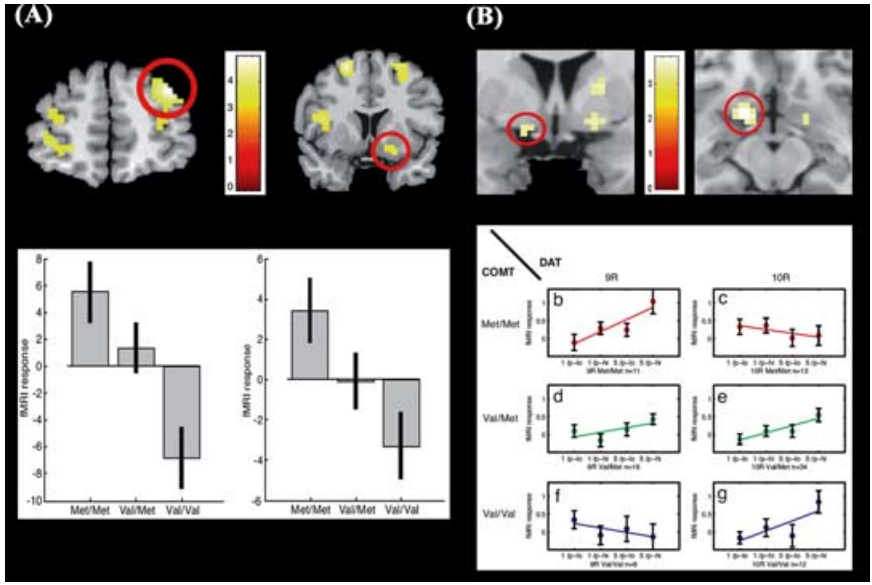

FIGURE 3. Genetic effects on brain response during reward anticipation. (**A**) Statistical maps overlaid onto structural MRI showing the effect of COMT genotype on reward anticipation–related activation in the prefrontal cortex (*left*) and the ventral putamen (*right*). Met/Met subjects (less enzyme activity) show highest activation levels, whereas Val/Val subjects show the lowest. (**B**) (*Up*) Functional interaction between COMT and DAT genotypes in the left ventral striatum. (*Down*) fMRI responses from the left ventral striatum as a function of reward probability (*p*-low vs. *p*-high), magnitude (1€ vs. 5€), and genotype. In all groups except DAT 10R COMT Met/Met and DAT 9R COMT Val/Val, activation increases according to probability and magnitude of rewards. The blunted response in DAT 10R COMT Met/Met and DAT 9R COMT Val/Val subjects may reflect suboptimal neural encoding of rewards. Reprinted and modified with permission from REF.[10] © (2007) The National Academy of Sciences.

most common.[171] Although this configuration does not affect the corresponding protein's structure, it does influence gene expression[172–174] and protein availability.[175–177] Despite the somewhat controversial results, there seems to be stronger evidence for higher DAT availability and gene expression related to the 10-repeat allele, which would lead to lower dopamine levels. Moreover, disruption of the DAT gene in DAT-knockout mice has been shown to alter their "social" behavior.[178]

A recent study assessed the effect of COMT and DAT genotypes on anticipation of monetary rewards that varied in probability and magnitude.[10] Neuronal activity in the prefrontal cortex and in the striatum was modulated by the COMT genotype. Subjects homozygous for the Met allele, and thus with presumably greater dopamine availability, showed larger responses to anticipated rewards than those who were homozygous for the Val allele. Activation in the ventral

striatum was also scaled as a function of both reward probability and magnitude, but this activation was affected by neither the COMT nor DAT genotype independently. However, the results found an interaction effect between the two genotypes. This effect came from the fact that subjects homozygous for the Met allele and for the 10-repeat allele and subjects homozygous for the Val allele and carriers of the 9-repeat allele showed a weakened striatal response to increasing expected values, suggesting a nonoptimal reward encoding (FIG. 3). This observation is consistent with the notion that both very low and very high dopamine levels are detrimental for some cognitive functions as, for example, working memory.[179]

In a recent study, we have also observed synergistic effects of COMT and DAT genotypes.[180] These effects are found in the ventral striatum and the DLPFC during anticipation of uncertain rewards and in the lateral OFC at reward delivery. Subjects homozygous for the Met allele and carriers of the 9-repeat allele exhibited the highest activation, presumably reflecting a functional change consecutive to higher synaptic dopamine availability.

In conclusion, there is now compelling evidence that genetic variations in dopamine-related genes modulate the physiological response of the dopaminergic system, which may help explain the interindividual differences commonly observed in compulsive behavior, such as pathological gambling and drug addiction, and vulnerability to neuropathologies (e.g., schizophrenia).

CONCLUSIONS

In recent years, the combination of molecular genetics, endocrinology, and neuroimaging with economic and social theories has provided many data that help in understanding the biological mechanisms influencing reward processing and social interaction. These studies have demonstrated that genetic and hormonal variations affecting dopaminergic transmission affect the physiological response of the dopaminergic system and its associated cognitive functions, and that these variations may account for some of the interindividual and intraindividual behavioral differences observed in reward processing and social cognition. Although this review emphasizes biological influences on reward-related behavior and social interactions, complex behaviors such as social interactions result from the interplay between genetic and environmental influences. Genes provide the foundation of behavior, but environmental traits and early experience play an important role in modulating the expression of these behaviors through their effect on the underlying physiological mechanisms.[181]

In conclusion, the multilevel analysis used in social neuroscience has now proved to be a useful approach for assessing the neurobiological mechanisms underlying variations in social behavior. Identifying the molecular and cellular markers of reward processing and social interaction provides new insights into

the basic mechanisms underlying interindividual differences in susceptibility to disorders such as pathological gambling and drug addiction.

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