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Understanding Interpersonal Function in Psychiatric Illness Through Multiplayer Economic Games

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Abstract

Interpersonal factors play significant roles in the onset, maintenance, and remission of psychiatric conditions. In the current major diagnostic classification systems for psychiatric disorders, some conditions are defined by the presence of impairments in social interaction or maintaining interpersonal relationships; these include autism, social phobia, and the personality disorders. Other psychopathologies confer significant difficulties in the social domain, including major depression, posttraumatic stress disorder, and psychotic disorders. Still other mental health conditions, including substance abuse and eating disorders, seem to be exacerbated or triggered in part by the influence of social peers. For each of these and other psychiatric conditions, the extent and quality of social support is a strong determinant of outcome such that high social support predicts symptom improvement and remission. Despite the central role of interpersonal factors in psychiatric illness, the neurobiology of social impairments remains largely unexplored, in part due to difficulties eliciting and quantifying interpersonal processes in a parametric manner. Recent advances in functional neuroimaging, combined with multiplayer exchange games drawn from behavioral economics, and computational/quantitative approaches more generally, provide a fitting paradigm within which to study interpersonal function and dysfunction in psychiatric conditions. In this review, we outline the importance of interpersonal factors in psychiatric illness and discuss ways in which neuroeconomics provides a tractable framework within which to examine the neurobiology of social dysfunction.

Keywords

Decision making; interpersonal function; multi-agent games; neuroeconomics; psychiatric illness; social neuroscience

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At least three prominent psychiatric conditions are characterized by difficulties in interpersonal functioning: borderline personality disorder (BPD; and the personality disorders more generally), autism, and social phobia. Individuals with BPD have unstable and intense social relationships (1) and exhibit social problem-solving deficits (2,3), and "frantic efforts to avoid abandonment" is the DSM-IV criterion for BPD with the highest specificity and positive predictive power (4). Social impairments are also included in the imperative criterion of autism spectrum disorder (ASD) (1), and individuals with autism display minimal social reciprocity and exhibit limited interest in social interactions (5,6). In social phobia, individuals experience debilitating fear of judgment or embarrassment in interpersonal situations that contributes to avoidance of social interactions (1,7,8). This is by no means an exhaustive list, and several other psychiatric conditions are defined in part by interpersonal difficulties (e.g., paranoid schizophrenia [1], psychopathy characterized by patterns of manipulating others' emotions and lack of empathy and, in children, conduct and oppositional defiant disorder characterized by aggression and defiance toward others; for review, see Blair *et al.* [9]).

In other psychiatric conditions, interpersonal dysfunction is not an imperative criterion but rather a debilitating sequela of illness. For example, individuals with major depressive disorder report greater distress from interpersonal difficulties (10), more negative interactions with partners (11), fewer social supports (12), and impaired family functioning (13) relative to control groups. In comparison, those with posttraumatic stress disorder (PTSD) exhibit anger and interpersonal aggression as complicating factors in social relationships and critical barriers to effective treatment (for meta-analysis, see Orth and Wieland [14]). Anger and aggression affect the therapeutic process, particularly among those with combat-related PTSD (15-17), and damage interpersonal relationships that are essential to the social support necessary for recovery of functioning (18-27).

As an essential first step, the foregoing data provide excellent descriptive accounts of critical domains of interpersonal dysfunction in psychopathology, from social withdrawal in major depression to an impaired ability to make social inferences in autism. Equally apparent from this work, however, is the conspicuous absence of a unifying framework within which to programmatically examine the interpersonal difficulties seen in psychiatric illness. Neuroeconomics, and quantitative/computational approaches to social behavior more generally, provides a conceptual framework that facilitates explanatory insights into the interpersonal phenomena and associated neurobiology that accompany psychiatric illness.

Multiplayer Games and Learning Models Facilitate a Computational Neuroscience of Social Behavior

In many ways, the late arrival of interpersonal anomalies to a biological understanding of psychiatric illness is not surprising— social signals are a vast and difficult domain to quantify and parameterize. However, converging interest from a variety of fields—from behavioral economics to machine learning to psychology and neuroscience—is bringing a powerful set of tools to bear on the understanding of basic neural computations of social interaction and, by extension, pathologies of social behavior (see also Hasler [28] and our related discussion in Kishida *et al.* [29]). Here we outline advances in two areas, behavioral economics and machine learning, that provide traction for understanding social behavior and the neuroscience of how it breaks down in psychiatric illness.

Behavioral Economic Approaches to Social Behavior

For more than half a century, mathematicians and economists have studied how humans make decisions with, about, and among one another (30). These decisions are often studied as utility-maximizing choices made within structured economic settings, and the underlying phenomena have been of common interest to social psychologists and behavioral economists alike: prosocial behavior, social influence, social biases, norm violations, interpersonal relations, and group dynamics. Two features of behavioral economics recommend it to the study of social behavior and its pathologies. First, behavioral economics offers a rich set of well-characterized paradigms with which to evaluate social interactions (31). An even greater contribution, however, lies in the quantitative performance benchmarks for behavior that accompany these paradigms. That is, economics offers mathematical depictions of interpersonal dynamics, and in doing so suggests mechanistic accounts of normative social behavior against which pathological dynamics and neural function can be verified or dismissed. This contribution is critical, as mathematical models of social behavior represent an intermediate level of description that has the potential to link social phenomenology to neurobiological mechanisms, not unlike the role that psychophysical models in vision science have played in explaining visual illusions in terms of their underlying neurophysiology (e.g., apparent motion illusion in terms of adaptation of receptive fields) (32).

Behavioral economic methods for examining social behavior typically extend from game theoretic principles. Game theoretic paradigms or “games” consist of a set of participants (“players” or “agents,” each with “preferences”), a set of behavioral options (“strategies”) available to those players, a formalized structure including “order of moves,” a specification of outcomes (“payoffs”) for each combination of strategies, and task instructions (“information”) that provide participants with payoff-relevant variables. By varying the strategies, payoffs, and structural features of these interactions, seemingly simple exchange games can be adapted to elicit and evaluate an assortment of social phenomena—from discrimination to prosocial behavior, and intergroup dynamics to high order social cognition (33-36). A variety of multiagent economic games have received attention for their utility in parsing the behavioral dynamics associated with social preferences (e.g., fairness instincts in ultimatum, dictator games) and strategic cooperation and competition (e.g., prisoner’s dilemma, stag’s hunt, trust games). Social interactions elicited in the context of these games can be modeled and then related to measures of neural activity, using tools such as positron emission tomography (37), functional magnetic resonance imaging (38), near infrared spectroscopy (39), and electroencephalography (40).

For example, in neurotypical participants, much progress in understanding neural signals critical to trust and cooperation has been made using variants of a simple trust game (41,42). In a trust game, an individual has the opportunity to entrust a valued resource (often money) in a social partner, with the hope that the partner will repay that trust with a return on their investment. Trust can thus be operationalized as the amount of resources invested, and trust or cooperation between individuals develops and is maintained when trust is repaid. When trust is broken, cooperation falters. This basic paradigm was used in one of the first functional neuroimaging studies in which interacting participants were scanned simultaneously and identified neural responses that predicted intention to trust and reputation formation (38). The trust game has now been used in neuroimaging studies as a sensitive and parameterized assay of many aspects of trust and cooperative exchange (43-48).

Machine Learning Approaches to Social Behavior

Machine learning approaches, particularly reinforcement learning, have been increasingly applied to multiagent games to describe the mechanisms by which humans learn, navigate, and make choices in social environments (for review, see Behrens *et al.* [49]). In basic reinforcement learning, individuals have expectations about the values associated with potential actions, and ongoing differences between predicted and obtained outcomes ("prediction errors") dynamically update action-value pairings and influence subsequent decisions ([50-56]; for discussion of the utility of reinforcement learning models for understanding psychiatric illness, see Montague *et al.* [57] and Maia and Frank [58]). Social actions are similarly drawn from a behavioral repertoire (e.g., share, cooperate, defect) and have intended effects and associated outcomes that change over time and social context. Reinforcement learning approaches can thus be applied to multiagent settings to test specific variables that contribute to interpersonal dysfunction (e.g., value of one's own social decisions, value of a partner's actions, learning social action-value pairings, updating social expectations, etc.).

Using this approach, Behrens *et al.* (59) as well as Burke *et al.* (60) found that learning from personal experience and learning from social partners combine to influence decisions through separable neural learning signals reflected in hemodynamic activity in ventral striatum and prefrontal cortex (PFC). Learning in social environments can also incorporate rich scenarios that take into account the mental states of others. For example, when an employer decides to check (or not) the work of an employee, a value calculation is made: it is costly to take the time to check the work, but checking may induce the employee to do better work in the future if s/he thinks the employer will keep checking. In this way, the value of checking depends, in part, on how the employer believes the action will influence the future choices of the employee. Computational models have begun to delineate neural signals that track beliefs about the mental states of others in diverse social settings, including this "work or shirk" dilemma (61), games of cooperation (62,63), bargaining (64), and competitive learning (65). As outlined below, these models applied to multiplayer games are relevant for examining the role of social inference and its underlying neurobehavioral mechanisms in interpersonal impairments associated with psychopathology.

Multiplayer Economic Games Quantify the Behavioral Dynamics and Neurobiology of Social Difficulties in Psychiatric Illness

Neural signals measured in real-time interpersonal interactions combined with formal computational models of social dynamics, provide powerful tools with which to explore normative and abnormal social behavior. The framework is ostensibly simple: to understand the neurobiology of social dysfunction, one must measure neural activity as participants engage in social interaction or make social decisions. However, social interaction and psychiatric illness are each uniquely difficult to assess because the state space of social behaviors is vast, and there are few external indicators of psychopathology beyond self-report and symptoms ascertained through clinical interviews or behavioral observation to aid in objective psychiatric diagnosis.

Multiplayer economic games provide one tool to evoke, monitor, and measure the degree and type of social impairment in distinct psychiatric illnesses. As noted earlier, one significant contribution of behavioral economics is quantitative performance benchmarks for social behavior. Specifically, measurements from individual subjects can be compared against these metrics, and these benchmarks can be used to design realistic social partners. Although the preferred players for basic behavioral economics paradigms are naïve human participants interacting with each another, computer agents designed to play like humans can be generated by (i) sampling large normative data sets of human-human interactions or (ii) implementing algorithms that play predetermined strategies. Such “partners” can be particularly useful when the degree of freedom is the (psychiatric) participant, rather than the dyad or group, and the standardization of partner behavior is needed. Below, we review recent studies from our group and others that illustrate the utility of neuroeconomic approaches with varying types of interactive partners for understanding the aberrant social dynamics and attendant neurobiology that accompany a range of psychiatric disorders.

Borderline Personality Disorder

Unstable interpersonal relationships are among the most prognostic features of BPD (4). To examine the neurobehavioral mechanisms underlying these impaired social dynamics, we adopted an iterated version of the trust game in a large sample of individuals with BPD playing human partners and, relative to healthy participants, found anomalous neural responses to noncooperative gestures (66). That is, when cooperation begins to falter, healthy participants show increased hemodynamic activity in anterior insular cortex, and this neural response precedes an attempt to coax back cooperation from their partner. In contrast, individuals with BPD exhibit a relative insensitivity of insular cortex to level of cooperation and are less likely to attempt to coax back cooperation. This effect is specific in three ways. First, when inflicting noncooperative exchanges on social partners, both healthy and BPD participants show increased insula activity, highlighting that the insula in BPD is specifically insensitive to level of trust received and likely related to abnormal perception of social partners’ actions. Second, subsequent work showed the decreased trust to be specific to BPD when compared with individuals with major depression, a common comorbid condition of BPD (67,68). Finally, individuals with BPD differ from control groups when making decisions involving social risk (trust game), but not nonsocial risk (gambles) (67,68). Taken together,thisworkidentifiesanomaloussocial“input”perception(rather than “output”) as a potential mechanism of interpersonal dysfunction in BPD and recommends the accompanying neurobehavioral response to social risk as a biomarker specific to the disorder.

Psychopathy

Economic exchange games have also revealed a bias in the social norms of high-psychopathy individuals. Using a cooperation game known as the “prisoner’s dilemma,” Rilling and colleagues found that even after successful cooperation, dyads that included high-psychopathy individuals were more likely to lead to mutual defection relative to dyads with low-psychopathy players (69). Moreover, high-psychopathy individuals showed lower amygdala activity following defections, suggesting an impaired social learning process in which defections are not negatively reinforced. In another study, primary-psychopath participants behaved identically to individuals with frontal cortex lesions and were both (i) less generous to social partners in a dictator game and (ii) more likely to accept ungenerous offers in an ultimatum game (70). These games each assesses fairness norms, and these data suggest that noncooperative social gestures are the norm among high-psychopathy individuals and that neuroeconomic games may be useful in differentiating among subtypes of psychiatric conditions.

Social Anxiety

Distorted predictions and irrational expectations about social outcomes are a core feature of social phobia (1). Recent work indicates that these biased cognitions may derive from an inability to infer how a social partner will view one’s social actions. To examine this possibility, Sripada and colleagues (71) used a trust game to compare neural responses when individuals were considering the actions of a real social partner or the actions of a computer partner. Individuals with social anxiety disorder showed diminished activity for social relative to nonsocial partners in a region of medial PFC implicated in theory-of-mind (72). The nature of the inferential impairment in social anxiety likely differs from that observed in personality pathologies, and these data again exemplify that specific interpersonal abnormalities can be tested with a neuroeconomic approach.

Autism Spectrum Disorders

Diminished social reciprocity is a primary feature of ASD, and difficulty inferring the mental states of others has been posited to contribute to this impairment (1). In a behavioral study, Yoshida and colleagues adopted a game-theoretic approach to model this inferential process (63,73). Participants played a coordination game, known as a “stag hunt,” in which two players benefit from coordinating their actions. Successful coordination, however, depends on accurately inferring the strategy chosen by the social partner, which in turn may depend on the social partner inferring one’s own strategy. The depth of inferential sophistication differed between ASD and controls, each playing computer partners, providing one of the first demonstrations that computational models of social cognition can provide a mechanistic account of impaired social dynamics in psychiatric illness. In another relevant study, participants with autism played a modified dictator game in which they chose among options to donate (or not) to charity and did so while observed by others or in private. When observed by others, control participants made increased donation choices, whereas the autism group showed no social facilitation; the groups showed equal performance facilitation when observed during a nonsocial cognitive task, suggesting a specific insensitivity to social reputation in ASD (74).

Developing Quantitative Biomarkers Using Multiagent Economic Games

In addition to elucidating neurobehavioral mechanisms that underlie interpersonal dysfunction, multiagent games can be used to develop quantitative benchmark biomarkers in large control samples against which atypical behavior may be compared. As an initial step in this direction, we assessed participants with autism playing the iterated trust game with another human while undergoing functional magnetic resonance imaging scanning (75). Using principal components analysis of neural responses in cingulate cortex, we first developed basis sets from a large database of more than 100 control players (38,45) as normative standards against which to measure the social deficits associated with autism. We then projected the cingulate responses of the individuals with autism onto the normative basis sets, yielding a single metric per participant, and compared the projection coefficients between groups for each principal component. The projections differed only in one principal component and one condition, the “self” decision-making phase of the interactive game. The ASD cingulate cortex responses correlated with social symptom severity, and these data together strongly offer multiagent games as a way to elicit and identify possible social phenotypes.

In a recent analysis of behavioral data from 287 dyads playing the trust game, Koshelev *et al.* (76) implemented a related data-driven approach to assess whether healthy control players’ behavior could act as a “biosensor” to detect aberrations that differentiate among psychiatric diagnoses. Each of the dyads consisted of a healthy control investor and a trustee who had been a priori diagnosed with one of several psychiatric conditions. Classification analyses applied to the interactive behavior from the game identified four unique clusters, each of which was overrepresented with “biosensor” investors who had played partners with one of four unique diagnoses. Krajbich and colleagues (77) further tested the social emotions of “guilt” and “envy” in patients with ventromedial PFC lesions using a formal economic model of choice applied to behavior from a battery of two-party exchange games (ultimatum, dictator, and trust games). The model incorporated terms for aversion or affinity for unequal payoffs, with parameters that allowed indexing of social behaviors normally evoked by guilt and envy, and the authors observed a specific insensitivity to the guilt parameter in the patient group. Social emotions require the presence of or comparison with another social agent (e.g., envy exists only by virtue of social comparison), and parametric quantitative models facilitate a mechanistic understanding of specific aspects of interpersonal exchange that contribute to disparate anomalies in social interaction.

Thus, interactive economic paradigms can be applied fruitfully to study interpersonal dysfunction in at least two ways. First, these paradigms provide a formalized framework within which social function and dysfunction, and their corresponding neuroscience, may be parameterized and explained. Second, these methods facilitate objective assays through which complex interpersonal phenomena may be reduced to quantitative biomarkers for use in genotyping and psychiatric assessment.

Multiagent Economic Games Identify Therapeutic Targets and Quantify Therapeutic Response in Treatment of Interpersonal Dysfunction

Finally, multiplayer economic games, and more generally computational or quantitative approaches to social function, can both point to targets for intervening on interpersonal impairments and be used to quantify the outcome of treatments. A few pioneering approaches have begun to suggest that, coupled with multiagent games, administration of neuropeptides, adjusting neurotransmitter availability, manipulation of neural responses, and behavioral approaches may aid in alleviating specific social impairments that accompany psychiatric conditions.

Kosfeld and colleagues (78) were among the first to implement this approach and demonstrated that intranasal administration of oxytocin, a neuropeptide that plays a key role in prosocial behavior, increases trust as quantified in monetary units transferred by investors to trustees in a trust game and was specific to when investors were transacting with human (versus computer) partners. These data suggested that oxytocin and other biologically informed agents may be used to alleviate interpersonal difficulties. Two initial forays into this area were reported by Andari *et al.* (79) and Bartz *et al.* (80) who administered oxytocin to individuals with autism and BPD, respectively. In individuals with autism who received oxytocin, Andari *et al.* (79) reported increased decisions to cooperate with a “good” partner on a decision-making task that dynamically changed the probabilities of cooperation from three fictitious players. The work of Bartz *et al.* (80) highlights the importance of considering symptom level differences in social function—in a modified prisoner’s dilemma game and patients with BPD, they observed no group differences between control and BPD participants following oxytocin administration, but found that oxytocin increased trust specifically in anxious BPD participants who sought intimacy, as evidenced by greater cooperative exchanges.

A handful of other studies have begun to use other exogenous methods to modify behavior in healthy controls participating in multiplayer economic games. For example, Knoch and colleagues (81) have shown that during the ultimatum game, transcranial magnetic stimulation to the right dorsolateral PFC reduces rejection of unfair offers although participants still perceive the offers as unfair, suggesting a diminished impact of self-interested motives on decision making. In the trust game, transcranial magnetic stimulation to right dorsolateral PFC reduced trustee repayments on high-investment trials, which the authors suggest reflects less concern for reputation formation and difficulty forgoing immediate benefits for potentially greater long-term gains (82). Also using an ultimatum game, Crockett and colleagues (83) showed that acute tryptophan depletion increases rejection of unfair offers, mimicking ventromedial PFC lesions and highlighting the role of the serotonergic system in interpersonal function. Purely behavioral manipulations can also have a strong impact on the dynamics of social exchange. For example, Kirk *et al.* (84) demonstrated that expert meditators are more likely to accept unfair offers and also exhibit diminished anterior insula activation along with enhanced activity in regions associated with perspective shifting and altruism (posterior superior temporal cortex and somatosensory cortex). Finally, Leiberg and colleagues (85) assessed the effects of an interpersonal behavioral therapy on social decision making and observed no impact of therapy on overall giving; instead, the treatment specifically increased helping behaviors when there was no chance the social partner could reciprocate. These studies highlight the translational potential of neuroeconomic paradigms for targeting, measuring, and modifying social dynamics or responses to social signals in psychiatric conditions.

Future Directions

As discussed here, the computational neuroeconomic approach provides a tractable starting point for a quantitative mechanistic understanding of healthy and impaired social signaling and how interpersonal difficulties may be measured and alleviated in psychiatric illness (31). Here we conclude with a few areas for future investigation.

Major depression and PTSD are among the psychiatric conditions with the most serious interpersonal sequelae. In depression, symptoms are prominently manifested in the social/interpersonal domain (e.g., increased negative interactions, diminished social supports, etc.), and individuals with PTSD show difficulties with emotion regulation in relationships that manifest as helplessness or anger/aggression. Social submission has been hypothesized to play a role in the etiology of mood and anxiety disorders (86,87), and one influential animal model of depression and anxiety is a social defeat model (86-89). These characteristics suggest that the social difficulties of mood and anxiety disorders may have roots in social valuation or social probability distortion that bias social learning and disrupt interpersonal function (e.g., social anhedonia or increased aggression due to diminished valuation of social rewards or social acts misperceived as threatening). Multiagent game theoretic paradigms that vary the probability and valence of specific interpersonal gestures may be a useful starting point from which these issues can be examined and against which animal models of social behavior can be validated.

Next, the influence of social peers has long been shown to affect an array of behaviors and choices (90,91), and social support strongly influences the onset and outcome of psychiatric illnesses (92,93). Indeed, research indicates that peer pressure to engage in activities that carry negative societal consequences increases in adolescence and then begins to decline in favor of behaviors that may not carry negative consequences but that are nonetheless shaped by one’s social peers (94). Recent work highlights the im-portance of social influence in both the onset and successful quit attempts of risk-taking behavior, including substance use, delinquency, and disordered eating patterns, particularly among adolescents (95). The neural substrates of susceptibility and resilience to peer influence in normative and psychiatric groups is ripe for investigation with neuroeconomic paradigms (see Burke *et al.* [96] and Chein *et al.* [97] for initial studies related to this area).

More generally, multiagent economic games provide a quantitative, biologically informed paradigm that allows a cross-diagnostic approach to understanding the interpersonal difficulties that psychiatric illnesses confer. This approach has begun to facilitate biomarker discovery and a mechanistic understanding of interpersonal impairments in psychopathology including biased social preferences, anomalous responses to positive and negative social gestures, failed attempts to repair negative interactions or facilitate positive interactions, and blunted social inference (63,66,75). Within this framework (Figure 1), social valuation (i.e., how much does one value specific social gestures), social risk preferences (i.e., how sensitive is one to social uncertainty), and social inference (i.e., how competent is one at inferring the intentions of social others) may provide unique discriminating vectors among distinct psychopathologies. As just a few examples, the social anhedonia seen in depression may signal diminished value from social interactions (whereas susceptibility to peer influence may signal excessive value), the fear of embarrassment in social anxiety may reflect impaired social risk assessment, and in autism, impairments in social inference may manifest as lack of social reciprocity.

In conclusion, psychiatric illnesses confer debilitating social difficulties, and computational/quantitative measures of social function deserve consideration as objective metrics for understanding the neurobehavioral roots of interpersonal dysfunction. Multiplayer games derived from behavioral economics coupled with neuroimaging and computational learning theory provide a paradigm that can be used to seek the underlying neurobiology and genetic correlates of social behavior, help differentiate diagnostic categories or assess criteria, or provide biobehavioral targets for novel treatment strategies to alleviate interpersonal difficulties.

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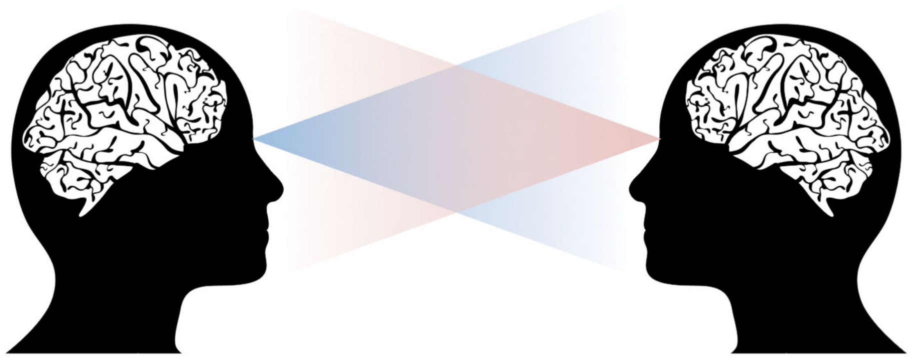

interpersonal decision-making	social inference	social valuation	social risk preferences
atypical interpersonal functioning	• theory of mind deficits • instrumental aggression	• increased or decreased interest in social activities • irritability toward social partners	• anxiety specific to social evaluation • paranoia about social partners
examples in psychiatric illness	• social impairments in autism spectrum disorders • psychopathic traits in antisocial personality disorder	• impulsive social behavior in mania • social anhedonia in depression • peer influence in substance use	• social phobia • distrust in borderline personality disorder • paranoia in psychotic disorders • aggression in PTSD

Figure 1.

Multi-agent economic games provide a tractable framework within which social decision-making and its neural computations may be quantified. (Row 1) These paradigms facilitate a cross-diagnostic approach to understanding the interpersonal difficulties that psychiatric illnesses confer. Within this framework, social inference (i.e., how competent is one at inferring the intentions of social others), social valuation (i.e., how much does one value specific social gestures), and social risk preferences (i.e., how sensitive is one to uncertainty in social contexts) may provide discriminating vectors for identifying specific impairments in social functioning (Row 2). For example, the lack of empathy in psychopathy may reflect a maladaptive use of social inferences, excessive valuation of social gestures may manifest as social impulsivity in bipolar disorder, and inaccurate perceptions of threat from social partners may contribute to aggression often observed with combat-related posttraumatic stress disorder (Row 3).