

Neuroeconomics: A Bridge for Translational Research

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Neuroeconomic methods combine behavioral economic experiments to parameterize aspects of reward-related decision-making with neuroimaging techniques to record corresponding brain activity. In this introductory article to the current special issue, we propose that neuroeconomics is a potential bridge for translational research in psychiatry for several reasons. First, neuroeconomics-derived theoretical predictions about optimal adaptation in a changing environment provide an objective metric to examine psychopathology. Second, neuroeconomics provides a “multilevel” research approach that combines performance (behavioral) measures with intermediate measures between behavior and neurobiology (e.g., neuroimaging) and uses a common metaphor to describe decision-making across multiple levels of explanation. As such, ecologically valid behavioral paradigms closely mirror the physical mechanisms of reward processing. Third, neuroeconomics provides a platform for investigators from neuroscience, economics, psychiatry, and social and clinical psychology to develop a common language for studying reward-related decision making in psychiatric disorders. Therefore, neuroeconomics can provide promising candidate endophenotypes that might help clarify the basis of high heritability associated with psychiatric disorders and that might, in turn, inform treatment.

Key Words: Endophenotypes, neuroeconomics, neuroimaging, psychiatric disorders, reward-related decision making, translational

Neuroeconomics is an interdisciplinary field that brings together psychology, economics, neuroscience, and computational science to investigate how people make decisions. Specifically, three basic questions are investigated (1). What are the variables computed by the brain to make different types of decisions, and how do they relate to behavioral outcomes? How does the underlying neurobiology implement and constrain these computations? What are the implications of this knowledge for understanding behavior and well-being in various contexts: economic, policy, clinical, legal, business, and others? Over the past decade, neuroeconomic work has focused on decision-making in healthy populations; however, there has been a steady increase in studies applying neuroeconomic methods to reward-related decision-making in psychiatric populations. The present special issue is intended to demonstrate the value of applying a neuroeconomics approach to the study of reward-related decision-making in social and nonsocial contexts with regard to psychiatric disorders across the lifespan.

We begin by emphasizing the need for improved treatments for psychiatric disorders and the need to develop a new nosological classification system that links pathophysiological variation at the level of brain systems to psychopathological variation at the behavioral phenotypic level. We point out that both these goals might be achieved by identifying a bridge for translational research, and we discuss how neuroeconomics might fulfill this role through its interdisciplinary nature and its unique combination of methods that allows the close mapping of reward-related decision making across multiple levels of explanation.

Beyond demonstrating the value of neuroeconomics for the study of reward-related decision making in psychiatric disorders, this special issue further intends to contribute to the ongoing process of demarcating the boundaries of neuroeconomics. During the *2011 Annual Conference on Neuroeconomics: Decision Making and*

the Brain, Scott Huettel, the outgoing president of the Society of Neuroeconomics, commented in his opening remarks that neuroeconomics, after 7 years since its first annual conference, is still referred to as a “nascent” discipline. Indeed, a quick glance at the neuroeconomic literature reveals the use of the word “nascent” to describe neuroeconomics in 2003 around the time of its formal inception (2), again 5 years later (3), and still in 2011 (1). That neuroeconomics is still a nascent field, combined with its interdisciplinary nature, poses a challenge for clearly defining it and demarcating its boundaries as a field. Throughout this special issue, authors at the intersection of neuroeconomics and psychiatry grapple with the definition and boundaries of neuroeconomics, and we hope that the special issue brings us closer to clearly defining this interdisciplinary field that holds much potential for psychiatry.

The Importance of the Problem

An estimated 57.7 million people (1 in 4 Americans) suffer from a diagnosable mental disorder (4). An increase in expenditures for mental disorders rising from \$35.2 billion in 1996 (adjusted for inflation) to \$57.5 billion in 2006 has been reported by the Agency for Healthcare Research and Quality. Fiscal societal strain has become an increasingly pressing concern as a result of treatment costs, reduced job productivity, and other indirect consequences of mental illness. For many, these costs do not compare with the emotional and social burden associated with mental illness, such as relational conflicts, low self-esteem, shame, and stigma.

Although we have made great strides in the last 50 years to develop appropriate treatments for psychiatric disorders, significant gaps remain (5). Not only are we discovering the limitations of current pharmacological and behavioral treatments for psychiatric disorders, but against the background of significant advances in brain sciences over the last 10 years, it has become increasingly recognized that the current nosological framework represented by the DSM-IV and ICD-10 exhibits serious shortcomings with respect to validity (6). In response, the National Institute of Mental Health Strategic Plan aims to “develop, for research purposes, new ways of classifying mental disorders based on dimensions of observable behavior and neurobiological measures” (7). In addition, in 2006 the National Institutes of Health established the new discipline of translational science to inform targeted treatment development. In this approach, basic science develops models for understanding normative behavior in healthy individuals. These models are then applied to psychiatric populations to identify biomarkers or endophenotypes that point to the mechanisms of attention, memory, and other higher cognitive processes underlying the behavioral pheno-

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types of psychiatric disorder. Biomarkers refer to characteristics that are measured objectively as an index of a pathogenic process or as a response to treatment (8), whereas endophenotypes refer to well-specified physiological or behavioral measures that occupy the terrain between disease symptoms (behavioral phenotypes) and risk genotypes (6). The final step in the translational approach involves the testing of the biomarker as a mechanism of change in clinical trials. For psychopathology, the modern translational goal is to explain mental phenomenon at multiple levels ranging from neurobiological to psychological but with enough detail so that consequences at one level induce testable predictions at another.

The Neural Circuitry of Reward and Its Relevance to Psychiatric Disorders

The neural circuitry of reward offers a promising functional domain (alongside other functional domains) for creating new ways of classifying mental disorders on the basis of dimensions of observable behavior and neurobiological measures. Empirical evidence (9–11) supports the potential of anomalous reward processing as a translational biomarker or endophenotype, and evidence is emerging in support of the role of reward-related brain function as a predictor of treatment response in psychiatric disorders (12). In the context of behavioral learning and motivational theories, rewards (positive and negative reinforcers) and punishment are thought to have three functions: they induce learning and exploration in the case of reinforcers, they facilitate approach or avoidance behavior, and they induce positive or negative emotions (13). Animal studies have identified the specific brain regions and pathways associated with the different functions of reward. These studies are reviewed in the articles by Chang *et al.* (14) and Montague and Kishida (15) in the current special issue and elsewhere (9,13,16,17). Animal studies have generally demonstrated dopaminergic single-cell firing rates modulated by primary rewards (e.g., food or juice squirts). These modulations show up directly in the ventral tegmental area and substantia nigra and indirectly in structures to which midbrain dopamine neurons project: within the basal ganglia, nucleus accumbens, and possibly the amygdala and orbital-frontal and prefrontal cortex (18). Human neuroimaging studies have confirmed that similar regions underlie human reward processing in response to a variety of primary (19) as well as secondary rewards, for instance, monetary (20) or social rewards (21).

Reward processing lies at the basis of learning and motivation, and disturbances within the reward system have been reported for all major classes of psychiatric disorders. One of the first classes of psychiatric disorder to be examined from a reward perspective is substance use disorders, because addictive substances induce effects similar to natural rewards. Not surprisingly, there is extensive evidence of hyper-responsivity to relevant cues within the mesolimbic reward system among addicted individuals (22). There is also evidence for the downregulation of striatal D2 receptor density among chronic stimulant users (23) and evidence of reduced striatal responsivity to nondrug rewards among substance-addicted individuals. Perhaps most interestingly (although least definitively), there is evidence that—among adolescents without significant drug use history but at very high risk of developing problems with addiction—there are identifiable on-average differences within the reward system (24). As discussed in detail by Monterosso, Piray, and Luo (this special issue [25]), establishing pre-morbid associations is a critical step with regard to establishing endophenotypes for addictive disorders.

Resemblances in the pathophysiology of reward between addictive disorders and pathological gambling (PG) have allowed for

the reformulation of PG as a nonsubstance-related addictive disorder (26,27). Recent reviews of neuroimaging studies in PG (28,29) have demonstrated that PG is associated with blunted mesolimbic-prefrontal cortex activation to nonspecific rewards, whereas these areas show increased activation when exposed to gambling-related stimuli in cue exposure paradigms.

Mood disorders are another class of psychiatric disorder for which altered reward processing seems to be an important correlate. In fact, Hasler *et al.* (30) identified impaired reward function as meeting more endophenotype criteria (31) for depression, compared with other putative endophenotypes. A central feature of major depressive disorder is a pervasive absence of motivation to obtain reward, low frequency of pursuing rewarding experiences, and reduced enjoyment of rewarding outcome (32). As reviewed by Ernst (current special issue [33]), these features of major depressive disorder are particularly devastating because of the clinical consequences of apathy, anhedonia, amotivation, and loss of interest in hobbies, socialization, work, food, and sex. Like substance use disorders and PG, this symptom cluster seems to be phenomenologically related to the putative functions of the mesolimbic dopaminergic projections from the ventral tegmental area into the ventral medial prefrontal cortex, amygdala, and ventral striatum (34). However, studies with depressed patients demonstrate deactivation in response to motivationally relevant stimuli usually associated with increased reward responses in healthy subjects. Thus, depressed individuals exhibit a kind of “motivational blindness” (10) for mood-incongruent (positive) stimuli, which at the very least maintain depression. This motivational blindness seems to be present in at-risk (but never-depressed) biological offspring of mothers with a history of depression (35), suggesting a potential causal role for disturbances in reward processing in the development of depression.

Abnormal dopamine-mediated responses to rewarding stimuli have also been demonstrated for schizophrenia, with the most salient abnormalities in the orbital and dorsal prefrontal structures that play a critical role in the ability to represent the value of outcomes and plans (9). With regard to attention-deficit/hyperactivity disorder (36), an increasing number of theoretical frameworks have incorporated altered reinforcement sensitivity as an important etiological factor in attention-deficit/hyperactivity disorder, and Sonuga-Barke and Fairchild (37) review some of these models in the current special issue. A growing literature focuses on the neural circuitry of reward in disruptive behavior disorders (e.g., antisocial personality disorder, psychopathy, conduct disorder, and oppositional defiant disorder). Psychophysiological, neuroendocrinological, and neuroimaging studies in externalizing disorders have traditionally tested theories of low arousal, sensation-seeking, fearlessness, stress responsivity, and more recently, empathy deficits (38). These theories can be easily related to motivational concepts, and recent studies (39–43) have begun to use behavioral economics and neuroeconomics to explicitly conceptualize these disorders within a reward framework. There have also been a growing number of studies examining the neural correlates of reward in personality disorders, pervasive developmental disorders, anxiety disorders, and research in children and adolescents as well as older adults (40–43). As reviewed by Hartley and Phelps (anxiety disorders [44]) and Delgado and Dickerson (disorders associated with old age [45]), neuroeconomics might be a very promising field of application, not only to address the lack of reward-related work in these areas but to highlight how other neural systems associated with psychopathology might interact with the reward system in the development or maintenance of disorders.

Neuroeconomics: A Bridge for Translational Research

Despite the great strides made by research examining the neural basis of reward processing in psychiatric disorders, several limitations exist that might be addressed by the application of a neuroeconomics approach. The first limitation of current research is not specific to reward processing but relates to the wider translational science approach. Cohen and Insel (46) pointed out that a major scientific obstacle that has impeded the translation of advances in cognitive neuroscience to clinical research and practice is that research instruments (e.g., functional magnetic resonance imaging tasks) are not always suitable “off the shelf” for clinical application and therefore might hinder progress in identifying clinically relevant biomarkers or endophenotypes. Tasks need to be robust and sensitive to produce reliable results in clinical populations, while having sufficient sensitivity to detect changes in clinical state necessary to assess the effects of treatment. Furthermore, tasks need to be feasible and appropriate for use in challenging populations. Lastly, there is not a single good case for a task that shows promise in a psychiatric population also being profiled in sufficient large samples of healthy individuals. In general, knowledge of normative responses in healthy populations is not well-enough characterized to permit the extraction of useful individual difference measures—a key if new cognitive tasks (and their brain response correlates) are to be useful in real-world clinical settings.

These scientific challenges are exacerbated by sociological challenges. Basic scientists responsible for developing experimental tasks are often neither interested in nor rewarded for translating these paradigms into clinically useful instruments, whereas clinical researchers and practitioners who could make productive use of such instruments rarely have the relevant training in behavioral and neuroscientific methods to pursue such work (46). Moreover, there is a lack of crosstalk between the fields of psychology, cognitive neuroscience, neuroanatomy, and computational science. In other words, as stated by Cohen and Insel, translational research in cognitive neuroscience is in need of a translator. Although this aim can be achieved with the establishment of incentive and funding opportunities for investigators and programs, this aim might also be facilitated by the creation of new disciplines where researchers from multiple fields can converge. In the context of reward research, we propose that neuroeconomics is a field that shows immense promise as a potential bridge for translational science.

Neuroeconomics is concerned with questions about how we make choices (i.e., decision making). Decision making refers to the process of using preferences, selecting and executing actions, and evaluating outcomes (11). Even the most basic and seemingly inconsequential decisions can be very complex. It is therefore not surprising that a discipline that might optimally elucidate such a complex process should owe its existence to the interaction of several parent disciplines—each of which in its own right underwent significant changes in the last half of the 20th century (47). The first set of shoulders that neuroeconomics stands on is the field of behavioral economics, led by Kahneman and Tversky, which challenged some of the assumptions in neoclassical economics during the 1960s and 1970s. A central concept in neoclassical economics used to explain economic behavior is that of “utility.” Briefly, as Marshall (48) wrote in 1920 (p. 78): “Utility is taken to be correlative to Desire or Want. It has been already argued that desires cannot be measured directly, but only indirectly, by the outward phenomena to which they give rise: and that in those cases with which economics is chiefly concerned the measure is found in the price which a person is willing to pay for the fulfillment or satisfaction of his

desire.” Preferences are therefore thought to be revealed through choice behavior governed by normative algorithms about how information was processed in making decisions. The innovation led by Kahneman, Tversky, and others used ideas from psychology to demonstrate the limits of these normative principles (i.e., normative principles fail in many instances to predict the actual choice behavior of humans).

In parallel, cognitive neuroscience was undergoing a revolution due to the development of brain imaging technology that could map brain and mind functioning more proximally. Animal studies (as discussed in the current special issue by Chang, Barack, and Platt [14]), in particular the work of Newsome and Glimcher, took the first steps towards demonstrating the correlation between neuronal activity and choice behavior in monkeys. Building on early work by Shizgal (49,50), Platt and Glimcher (51) formalized for the first time an economic-mathematical approach for the physiological study of decision-making, which pointed to potential neurobiological constraints on the algorithmic processes involved in decision making described by behavioral economists (52). It is at this point in the development of behavioral economics and cognitive neuroscience that the new field of neuroeconomics was born. For the first time, behavioral economic tasks, combined with neuroimaging techniques in humans and single-cell recordings in nonhuman primates, could be used to conduct algorithmic analyses of the “physical mechanisms” of choice in the brain. As it turns out, the physical mechanisms of choice in the brain seem to be largely located in the reward system of the brain. Getting back to the concept of utility, we can think of the reward system of the brain as a “global valuation system,” with dopamine as the common currency. In other words, for the first time we might be able to describe how neurons think in the same language we describe how the brain thinks at a neural network level. It is important to understand therefore that what we mean with neuroeconomics is not the same as what is meant with fields that developed in the aftermath of neuroeconomics, for instance “neurolaw” or “neuroethics.” With neuroeconomics we do not mean the “the neural basis of economic decision making” (as in the “neural basis of legal decision making” or the “neural basis of ethical decision making”). Rather, we mean with neuroeconomics the infusion of neuroscience with how economics models value and utility. In neuroeconomics, we use economic metaphors to study how neurons and neural networks make decisions. Therefore the excitement generated by neuroeconomics is because the metaphor of utility and value can be used across the different levels of explanation from cells to society, making this a rather unique field. In applying this metaphor to psychiatry, we might then hypothesize that disturbances in the global valuation system of the brain is a major cause of psychiatric disorder (53). Depending on the task constraints, such disturbances might be evident in increased or reduced brain activation in reward-related areas or might even be reflected in altogether alternative (categorically different) decision-making strategies, for instance, the use of an altogether different reference point such that relative gains and losses are valued differently.

At this juncture it is important to highlight the boundaries of neuroeconomics. We do not believe that decision making (and associated aberrations in reward processing) underlies all of cognitive functioning and can explain the full behavioral phenotype of all psychiatric disorders. Decision making (the main focus of neuroeconomics) includes preference formation, action selection, and execution and evaluation of outcomes. This stands in contrast to other processes that are orthogonal to valuation—for instance, theory of mind reasoning. Theory of mind could be seen as logically anteced-

ent to valuation. A pathology that undermines theory of mind of course affects value and choices but not because of anomalous processing within the valuation system. The child that anticipates that “Maxi will look for the chocolate” where the child herself knows it to be hidden rather than where Maxi originally saw it need not have any abnormality in valuation *per se*. We can therefore expect that, given that behavior results from a multitude of interacting cognitive processes, suboptimal reward processing is only one of several putative disease mechanisms or endophenotypes that form part of the multiple pathways between the “upstream consequences of genes” and the “downstream traits of clinical phenotypes” (30).

Against this background, it is clear why neuroeconomics is promising for identifying reward-related biomarkers or endophenotypes in translational research. In addition, limitations in current reward-focused work in psychiatric disorders point to several other reasons for applying a neuroeconomics approach to psychopathology. First, although simple stimulus-response approaches to reward processing are useful for understanding basic approach and avoidance behavior, they do not reflect the dynamic nature of real life interaction with the environment. A major problem for those with psychiatric disorders is a difficulty responding to rewards in dynamic and context-appropriate ways. Neuroeconomic games allow for complex, dynamic (ecologically more valid) contexts to be created within which reward-related decision-making might be examined (54).

Also, basic neuroeconomic games allow for the modeling of the effects of beliefs and affect on reward processing. For instance, Delgado *et al.* (55) used a neuroeconomic game (trust task) to show that prior social and emotional information on trust game partners modulates reward responses in the brains of healthy adults. With the same neuroeconomic task, Sharp *et al.* (43) showed that modulation of insula responses was absent in the brains of boys with externalizing behavior problems. Similarly, King-Casas *et al.* (56) showed that the norms used in perception of social gestures are pathologically perturbed or missing altogether among individuals with Borderline Personality Disorder, with differential insula activation in these patients compared with normal control subjects. Findings such as these are made possible because neuroeconomic tasks can mimic to some degree the complexities and uncertainties of decision-making in a rapidly changing social world. Indeed, the contribution of neuroeconomic games might be the largest in the domain of social interaction (reviewed in this special issue by King-Casas and Chiu [57]) where social-cognitive research with traditional methods has struggled to find ways to approximate real-life social interaction with ecological validity.

Second, the increased salience that neuroeconomic tasks offer is further illustrated by inconsistencies found in reward studies of depression. In one study, happy facial expressions did not elicit reduced reward activation in depressed patients (58), which might be accounted for by reduced salience levels of the stimulus material used (10). In contrast to passive viewing tasks, neuroeconomic tasks are designed to more closely mirror the physical mechanisms of reward processing by tapping directly into utility functions and might therefore be more salient—for instance, where outcome-uncertainty during anticipation in a monetary reward task is probed (59).

A third advantage of applying neuroeconomic approaches to psychopathology relates to the fact that after 30 years since the first positron emission tomography study was published, there does not exist a single neuroimaging task that can be used to diagnose a psychiatric condition. For neuroimaging to fulfill this promise, it will be necessary to develop experimental approaches with better dis-

criminatory power with regard to disorder-specific pathophysiology. In practice, this means that the same experimental paradigms should be used across different patient populations in contrast to disease-specific paradigms. Because neuroeconomics provides a unified framework within which to operationalize decision making, these tasks are ideally fit to this purpose. Applying the same neuroeconomic games across disorders will advance clinical science by taking a first step in developing a new nosological classification system that links the variation of reward processing at the level of brain systems to psychopathological variation at the behavioral phenotypic level. Neuroeconomics might therefore provide standardized methods for indexing brain function that reflect the physiological processes of the reward system that are linked to the behavioral and cognitive deficits observed in mental disorders. We might therefore imagine a world where disorders are classified on the basis of ways that underlying biological mechanisms fail, reward processing being only one such mechanism. The use of the same neuroeconomic tasks across different disorders will also advance basic science by elucidating the fractionation of reward components. Of course, the domain of reward processing might be just one of several brain systems by which to reorganize psychopathology at the behavioral phenotypic level, alongside other functional domains.

Conclusions

Neuroeconomic methods combine behavioral economic experiments to parameterize aspects of reward-related decision-making with neuroimaging techniques to record corresponding brain activity. In this introductory article to the current special issue, we propose that neuroeconomics is a potential bridge for translational research in psychiatry for several reasons. First, neuroeconomics-derived theoretical predictions about optimal adaptation (adaptive goal achievement) in a changing environment provide an objective metric to examine psychopathology as suboptimal behavior (53). Second, neuroeconomics provides a “multilevel” research approach that combines performance (behavioral) measures with intermediate measures between behavior and neurobiology (neuroimaging) and uses a common metaphor to describe decision making across multiple levels of explanation. As such, ecologically valid behavioral paradigms closely mirror the physical mechanisms of reward processing. Third, neuroeconomics provides a platform for investigators from neuroscience, economics, psychiatry, and social and clinical psychology to develop a common language for studying reward-related decision making in psychiatric disorders. Therefore, neuroeconomics can provide promising candidate endophenotypes that might help clarify the basis of high heritability associated with psychiatric disorders and that might, in turn, inform treatment. Like any new interdisciplinary field, neuroeconomics is not without its weaknesses. Authors invited to contribute to this special issue have been asked to comment on disorder-specific limitations of neuroeconomics and outline plans for future research to address these limitations.

We thank the authors who have contributed to this special issue as well as the editors and external reviewers of *Biological Psychiatry*. The reviews presented here highlight what has been accomplished since the birth of neuroeconomics—a field that is only 1 decade old. It also serves as a useful foundation on which future research can be built. The application of neuroeconomics to psychopathology has only just begun.

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