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Review

Can the neuroeconomics revolution revolutionize psychiatry?

Gregor Hasler

Psychiatric University Hospital, University of Berne, Bolligenstrasse 111, 3000 Berne 60, Switzerland

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ABSTRACT

Neuroeconomics is a rapidly growing new research discipline aimed at describing the neural substrate of decision-making using incentivized decisions introduced in experimental economics. The novel combination of economic decision theory and neuroscience has the potential to better examine the interactions of social, psychological and neural factors with regard to motivational forces that may underlie psychiatric problems. Game theory will provide psychiatry with computationally principled measures of cognitive dysfunction. Given the relatively high heritability of these measures, they may contribute to improving phenotypic definitions of psychiatric conditions. The game-theoretical concepts of optimal behavior will allow description of psychopathology as deviation from optimal functioning. Neuroeconomists have successfully used normative or near-normative models to interpret the function of neurotransmitters; these models have the potential to significantly improve neurotransmitter theories of psychiatric disorders. This paper will review recent evidence from neuroeconomics and psychiatry in support of applying economic concepts such as risk/uncertainty preference, time preference and social preference to psychiatric research to improve diagnostic classification, prevention and therapy.

Contents

1. Introduction

Economics, psychology and neuroscience are converging into a new, unified discipline referred to as neuroeconomics. The ultimate goal of neuroeconomics is to provide a single, encompassing theory of human behavior by understanding the processes that connect sensation and action, thus revealing the neurobiological substrate of decision-making (Glimcher and Rustichini, 2004). This theory can be used as a framework to study various psychological, social and neural systems including learning, movement, social cooperation, brain reward pathways and neurotransmitter systems. The increasing number of neuroeconomics papers published in leading scientific journals such as *Nature* and *Science* reflect the increased attention toward this new research discipline in the scientific community. The practical utility of neuroeconomics has yet to be determined, and its potential contribution to the field of economics is a matter of debate (Balleine et al., 2009). However, a growing number of experts consider psychiatry to be neuroeconomics' most promising field of application (Loewenstein, 1996; Rangel et al., 2008).

How much could psychiatry really benefit from neuroeconomics? Psychiatry research has a multifaceted history in terms of disease concepts and research methods. In the beginning of

E-mail address: gregor.hasler@puk.unibe.ch

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the 19th century, the field of psychiatry was mainly descriptive in nature. Janet (1889) and Freud (1905) were among the first to develop integrative bio-psycho-social theories to explain the causes, pathogenesis and symptoms of psychiatric conditions. These intuitive theories provided a theoretical framework and a great deal of explanatory power, contributing to the establishment of psychiatry as a respected clinical profession. Because the main assumptions of these theories could not be tested empirically at the time of inception, they facilitated dogmatism and devaluation of experimental inquiry that dominated psychiatry over decades and led to stagnation of psychiatric research (Kandel, 1998). The publication of the third edition of the *Diagnostic and Statistical Manual for the Classification of Mental Disorders* (DSM-III) in 1980 marked the official beginning of the current, 'atheoretical' phase of psychiatry, representing an important step in the fundamental redirection of the discipline toward a more scientific course. To provide reliable diagnoses for clinical practice, the DSM-III diagnostic criteria are based on clusters of clinical symptoms irrespective of etiology and pathophysiology. Using methods from epidemiology, sociology, psychology, pharmacology, neurobiology and genetics, this 'atheoretical' approach has provided large amounts of empirical data and important insights from specific perspectives. The lack of an encompassing conceptual framework, however, reduces the explanatory power of these data to comprehensively explain motivational forces in individuals diagnosed with psychiatric disorders. To bridge this gap, decision theory with transparent formal models and precise theoretical predictions could bring further scientific rigor to psychiatric research by providing a strong conceptual framework.

In this perspective paper, fundamental concepts from decision theory and related experimental neuroeconomics studies are reviewed and discussed in terms of their potential use as a framework for psychiatry research. Because we are mainly interested in the causes and pathogenetic pathways which can lead to acute states of distress, our focus will be on psychiatric risk factors as opposed to acute symptomatic distress. Given the rather non-specific risk factor profiles of psychiatric disorders and the high comorbidity among these disorders, specific DSM-defined disorders cannot be used as absolute reference points in psychiatric research (Hasler and Northoff, in press). As a result, most of our neuroeconomic hypotheses will not be disorder-specific but related to etiologically-associated groups of disorders.

2. Single-dimensional utility

Economists attempt to construct one single global formalism to describe all choice behavior. To this end, *utility* is defined as a measure of relative satisfaction. In expected utility theory, actual choice can be understood as if a single-dimensional utility index is maximized. These theories assume that subjects encode the values of all things (goods, services, leisure time, wealth) in abstract common units. From an evolutionary perspective, one might not expect the same brain systems responding to primary natural rewards such as water, food and sex to respond to abstract outcomes such as points in a computer game, which are not relevant for survival. However, there is convergent empirical evidence for a common representation of desirability in specific prefrontal brain regions (Chib et al., 2009; Critchley and Rolls, 1996). Together with many other investigations demonstrating neural correlates of utility in key regions of the valuation network (Plassmann et al., 2007; Tom et al., 2007; Weber et al., 2007), these results suggest that utility is useful concept for brain research. Given that the brain regions associated with utility (mainly the orbitofrontal and ventromedial frontal cortices, but also midbrain dopaminergic regions and their projection sites in ventral striatum, Fig. 1) are thought to be

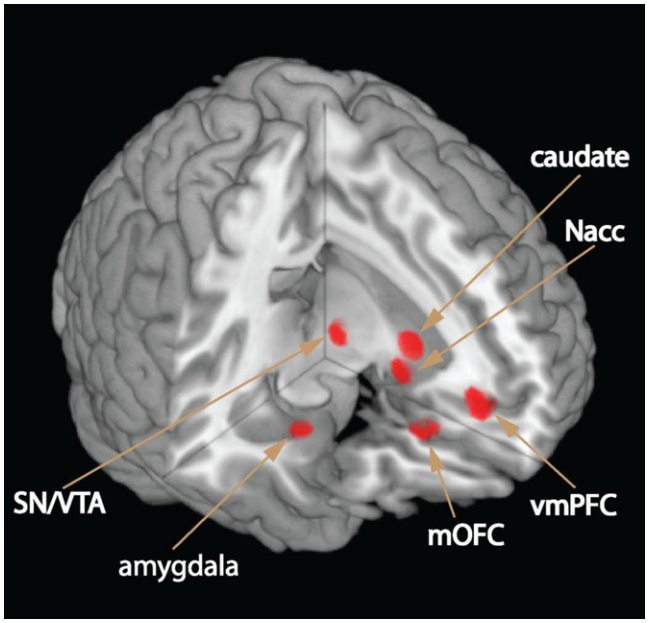

Fig. 1. Schematic illustration of the valuation network. Regions commonly implicated in evaluating rewards and risks in neuroeconomic imaging studies include dopaminergic neurons in the brainstem, such as substantia nigra (SN) and ventral tegmental area (VTA), which send projections to specific areas in the ventral striatum, such as the caudate nucleus and nucleus accumbens (Nacc). Dopaminergic projections also modulate neuronal activity in ventromedial Prefrontal Cortex (vmPFC) and medial orbitofrontal cortex (mOFC), which have repeatedly been shown to represent reward value. Figure was constructed by Jan Engelmann.

intimately involved in a wide range of psychiatric conditions characterized by emotional dysregulation (Hasler et al., 2006, 2004), one might hypothesize that dysfunction of this global valuation system is a major cause of psychiatric disorders. Three additional pieces of evidence support the notion that monoamine-related dysfunctions of a global valuation system contribute to a range of psychiatric conditions: (1) The monoamine neurotransmitters serotonin, norepinephrine and dopamine play important roles in the evaluation of rewards and punishments (Dayan and Huys, 2009). (2) At the same time, monoamine-modulating drugs demonstrate therapeutic effects in a wide range of psychiatric conditions including schizophrenia, mania, depression, obsessive-compulsive disorder, generalized anxiety disorder and panic disorder. (3) Finally, impairment of a global valuation/decision system could explain the fact that various psychiatric conditions co-occur in the same individual more frequently than expected by chance (e.g., up to 90% of individuals with obsessive-compulsive disorder also suffer from depression; (Hasler et al., 2005)).

Based on the assumption of an impaired global valuation system in psychiatric disorders, behavioral experiments using monetary incentives have been used to quantify psychopathology. Although lack of interest in natural rewards such as food and sex are considered key symptoms in depression, there is preliminary evidence that the lack of interest in money, a secondary reinforcer through which primary rewards can easily be acquired, can be used as a quantitative measure of depressive psychopathology. Specifically, there was a relatively strong correlation between depressive symptoms induced by experimental dopamine depletion and lack of interest in money as measured with the Monetary Incentive Delay task (Hasler et al., 2009a), suggesting that decision theoretic approaches are particularly well-suited for investigations of depression related to monoamine-deficiency. Alterations in the neural response to winning and losing money have been shown to be related to familial risk of depression (Gotlib et al., 2010), suggesting they are not mere consequences of the illness but

can occur before the onset of depressive symptomatology. These findings are important because they demonstrate that decision theory can be used not only to understand aspects of psychiatric disorders related to economic decision-making but also to elucidate causes and pathogenetic mechanisms of these potentially severe conditions. In addition, functional neuroimaging in combination with decision theory might be used as marker for specific psychiatric illnesses in the future, thus serving as a diagnostic tool.

While philosophers have historically considered utility as an indicator of a person's happiness, modern economists view utility as an abstract variable, indicating goal-attainment or want-satisfaction. A utility function has the following form:

$$U = f(x_1, x_2, \ldots x_n)$$

where x_1 to x_n all contribute to a person's utility. x_1 may represent food, x_2 furniture, x_3 leisure time, etc. A utility function is a method to assign a number to every possible consumption bundle such that more-preferred bundles get assigned larger numbers than less-preferred bundles. One might speculate that general lack of interest in individuals suffering from depressive disorders leads to a general decrease in utility, formalized as a monotonic transformation of the utility function. However, this would not change behavior because the magnitude of the utility function is only important as far as it ranks the different consumption bundles. It has been proposed that decisional anhedonia in depression reflects a shift in cost/benefit analyses (Treadway and Zald, 2011). Various types of evidence support this hypothesis. First, dopamine deficiency, representing a risk factor for depressive disorders (Hasler et al., 2008), may specifically increase the valuation of costs (Phillips et al., 2007). Such costs may involve time, effort, enduring pain and tolerating risk. Second, the anterior cingulate cortex, as part of the ventromedial prefrontal cortex, is necessary to invest additional effort for additional reward (Walton et al., 2007), and dysfunctions of this brain regions have appeared to be causally associated with depressive symptoms (Mayberg et al., 2005). Third, effort-based decision-making has empirically been related to trait anhedonia (Treadway et al., 2009), which is an important risk factor of depression.

The following are our global valuation system hypotheses of psychiatric disorders:

- Dysfunctions of the global valuation system increase risk for domain-non-specific psychiatric disorders such as depression and non-phobic anxiety disorders.
- Exaggerated valuation of costs is a specific risk factor for depression.
- The neural substrate of impaired effort-based decision-making in depression includes dopamine deficiency and dysfunctions of the ventromedial prefrontal cortex.

3. Marginal rate of substitution

Some psychiatric problems are surprisingly domain-specific. Patients with an eating disorder may initially refuse to eat any food. However, once this food abstinence leads to a pathologically low body weight, these patients may start to binge-eat. To avoid gaining weight such individuals may start vomiting and take laxatives. Later they may store large amount of foods in hidden places in the house and develop rituals to control the fear of foods. Although their clinical symptoms are multifaceted and vary considerably over time, food, eating and body weight are their exclusive focuses (Milos et al., 2005). Domain-specific symptoms are associated with domain-specific genetic risk factors (Kendler et al., 2007) and, on average, do not respond as well as domain-unspecific mood and anxiety symptoms to monoaminergic drugs, indicating important differences in etiology and pathophysiology.

One way to treat domain-specific psychiatric problems is by substitution, e.g., substitute consumption of a problematic good by a less problematic one. For example, in drug abusers, heroine is replaced by the less harmful drug methadone; the dependent adult son must learn to substitute his mother with people his own age; and the compulsive shopper must find less expensive ways to produce the same positive emotion. Many patients, however, show an impressive resistance to this type of substitution. Freud assumed that fixation of the libido to an early developmental stage or a certain type of early object leads to psychopathology (Freud, 1905), this implicating a deficit in the ability to substitute libidinal rewards as a major cause of neurosis and perversion.

Economists offer several scenarios to explain low marginal rates of substitution. First, by definition, if the subjective value of the problematic good is perceived to be much higher than the values of all unproblematic goods, individuals would not willing to exchange the problematic good for unproblematic goods. Indeed, a consistently positive response to a drug of abuse without experiencing associated aversive drug effects in subjects with low alternative pay-off probabilities (e.g., due to low educational status) represents a high risk for drug dependency (Davidson et al., 1993; Swendsen et al., 2009). The pharmacological effects of addictive drugs may further increase the relative value of the addictive drug by diminishing brain's sensitivity to drug-unrelated rewards (Goldstein et al., 2007).

Second, consumption of problematic goods (alcohol, drugs of abuse, commercial sex, etc.) is usually more certain (i.e., available at any point in time) than consumption of unproblematic "goods" (good times with loved ones, success at work, etc.). As a result, individuals may be unwilling to trade problematic goods for unproblematic ones in order to avoid consumption uncertainty (see Section 5).

Third, some patients are unwilling trade their problematic symptoms because they consider them to be part of their identity. This is quite common in personality disorders and paraphilias and may represent an extreme version of the endowment effect. In behavioral economics, the endowment effect is the observation that people increase their assessment of the value of a good once they own it, as evidenced by an increased aversion to loosing it. Behavioral experiments have shown that the endowment effect is an aversion to giving up a good rather than the pleasure of owning it (Kahneman et al., 1990). The endowment effect is associated with a discontinuity in the marginal rate of substitution, i.e., a discrepancy between the high minimal *willingness to accept* to give up a good they own and the low maximal *willingness to pay* to acquire it (Tversky and Kahneman, 1991). Gain-loss asymmetry (Section 6) is thought to be one mechanism underlying both the endowment effect and the willingness-to-accept/willingness-to-pay discrepancy. One consequence of this discrepancy is the retention of the status quo, which may represent an important obstacle to behavioral change in psychotherapies. Interestingly, depressed mood can reduce the endowment effect (Lerner et al., 2004), possibly explaining the clinical observation that secondary depression can lead to reductions of domain-specific psychopathology.

Fourth, psychiatric symptoms may be considered as taboo values or sacred values that precludes them from trade-offs with other values (Hanselmann and Tanner, 2008). When people are asked to trade their sacred values for values considered to be secular, what has been referred to as "taboo tradeoff" (Tetlock et al., 2000), they experience strong negative emotions such as anger, disgust and moral outrage and become insensitive to a logical cost-benefit analysis of the exchange. For example, when individuals with anorexia are asked to compromise their flat stomach, which could be considered as non-negotiable taboo value, in order to

prevent risk of serious health problems such as osteoporosis and cardiac arrhythmia, these individuals may turn into seemingly irrationality decision makers.

Neuroeconomists have begun to investigate the neural substrate of marginal substitution rate calculations (Knutson et al., 2007; Plassmann et al., 2007) and loss aversion (Tom et al., 2007). The link between loss aversion and amygdala activity (De Martino et al., 2010; Weber et al., 2007) may be particularly relevant to psychiatry because abnormal amygdala function has been found to be one of the most consistent neural correlates of affective disorders (Drevets, 2003). In other studies, loss aversion has been associated with changes in activity within dopaminergic targets in the ventral striatum (Kobayakawa et al., 2010; Tom et al., 2007). Specifically, the ventral stiatum and ventrolateral PFC showed steeper correlations with losses compared to gains, a finding that was interpreted as a marker for neural loss aversion (Tom et al., 2007).

In psychiatry, dopamine has been associated with the adjustment to changing stimulus-reward contingencies (Hasler et al., 2009b). Furthermore, dopamine depletion-induced deficits in reward learning has been associated with the risk of eating disorders (Grob et al., in preparation), which may explain the risk of "fixation" to oral rewards in these individuals. There is a wealth of data in animals demonstrating that drugs of abuse impair synaptic plasticity in the mesolimbic dopamine system (Kauer and Malenka, 2007). In a rat model of cocaine addiction, animals that progressively developed the hallmarks of addiction had permanently impaired neuroplasticity, as evidenced by long-term depression of synaptic transmission, whereas neuroplasticity progressively recovered in non-addicted rats that maintained a controlled drug intake (Kasanetz et al., 2010). Together, these data suggest that the ability to rescale synapses that were enhanced through strong immediate rewards, allowing them to encode future associations and restore flexibility to neuronal circuits, is necessary to adjust consumption as a function of environmental contingencies (availability of rewards, cost of rewards, etc.). In economic terms, mesolimbic neuroplasticity is required to maintain a reasonably high marginal rate of substation of "problematic" goods.

The following are our marginal rate of substitution hypotheses of psychiatric disorders:

- A low marginal rate of substitution for addictive goods is a risk factor for addiction.
- Impaired rescaling of synapses of the mesolimbic system is the neural substrate of a low marginal rate of substitution for addictive goods.

4. Expectation

The most common complaints of people suffering from stress-related psychopathology include negative experiences in the past and negative predictions about the future. Because expectations strongly influence their Pavlovian emotional responses and instrumental decision-making, we will now consider the nature of future expectations from a neuroeconomics perspective. A key theme emerging from research in this area is that numerous distinct types of expectation are formed in parallel within different brain systems.

Expected utility theory assumes that each available choice is evaluated based on both the probability and utility of its possible consequences. To this end, each choice is assigned one number – the 'expected,' or average, utility –, which can be compared with other choices. Maximization of the expected utility of gamble X can be formalized as follows:

$$\mathrm{EU}(X) = \sum_{x} p(x)u(x)$$

where $\mathrm{EU}(X)$ is the expected utility of gamble X, given probability p and utility u of payoff x. The concave curve of the utility function (e.g., $u(x) = x^{\theta}$ with $\theta < 1$) implies that money and wealth are diminishing in value. The exponent θ is a parameter that describes the function's degree of curvature and serves as an index of an individual's degree of risk aversion, which is a key feature of this theory (see Section 5 for more details).

Intuitively, the subject may consult an internal model of the outcomes of each action, evaluating the action's probability and current utility. However, individuals' limited working memory and computation capacity make it unrealistic to assume that subjects can fully model the complex, indirect consequences of their actions, let alone calculate expected utility (Balleine et al., 2009; Dayan, 2008a). As a result, the brain must apply methods to simplify the decision-making process, allowing logical actions in the absence of a complete model. Empirical evidence for central dopaminergic activity as a prediction error signal (Montague et al., 1996) suggests that one brain system updates and uses *only* one number – the expected utility – without explicitly recalculating this based on a full model. The downside of this computational streamlining is that behavior becomes insensitive to changes in the subject's goal (i.e. the current utility of outcomes for the subject) (Dayan and Niv, 2008). Given that involuntary habits, i.e. reflective thoughts and actions that contradict the individual's declared goals, are acutely relevant to psychiatry, this perspective promises to clarify our understanding of the formation and maintenance of maladaptive actions (Dayan and Daw, 2008b; Graybiel, 2008). Preliminary evidence suggests that habit learning is indeed altered in patients with various psychiatric conditions, particularly in those with drug addiction (Pierce and Vanderschuren, 2010), eating and obsessive-compulsive disorder (Graybiel and Rauch, 2000). Maladaptive responses to negative outcomes (Murphy et al., 2003), hyposensitivity to positive outcomes (Pizzagalli et al., 2009) and attentional and mnemonic biases toward negative information (Hasler et al., 2004) may all contribute to aberrant habits. For example, such factors may support exaggerated habitual avoidance of inferred threats (Dayan and Seymour, 2009). To further understand patients' behavior, the expected utility of arbitrary 'actions' or decisions have been mentioned. One may equally define the subject's expected utility of *situations* or states (Balleine et al., 2009). This is relevant to understanding Pavlovian emotional responses (i.e. innate rather than arbitrary). One may ask if Pavlovian emotional responses, like instrumental choices, reflect crude simplifications made by the subject (Everitt et al., 2003). In fact, like instrumental learning, emotional responses are complex and multifaceted. There is evidence that some emotional responses are more a vague anticipation, reflecting just the valence of an impending outcome. In analogy to habits, these might be informed only by expected utility of the current situation or state. In contrast, other responses reflect explicit awareness of the specific outcome using a full predictive model (Everitt et al., 2003). A key goal of psychiatry should be to understand the balance of these systems to normal and abnormal expectations and actions.

One might hypothesize that a powerful model-based learning system is a protective factor against psychiatric conditions such as drug addiction, eating and anxiety disorders, in which cues control behavior out of all proportions to the desirability of the predicted outcomes. In support of this, dysfunctions of brain regions associated with sensitivity to specific outcomes, such as the orbitofrontal cortex (Burke et al., 2008) and the basolateral complex of the amygdala (Corbit and Balleine, 2005), have been importantly involved in the pathophysiology of these disorders.

The value subjects assigned to a situation may be aberrant in many ways. Deficits in Pavolvian fear conditioning have been found to contribute to overgeneralization of negative predictions and chronic anxiety (Grillon, 2002). Such deficits may arise from

impaired neuroplasticity in the amygdala, anterior insula and anterior cingutlate cortex (Buchel et al., 1998). Additionally, impaired Pavlovian-instrumental transfer has been proposed to contribute to reductions in motivated behavior in depression (Talmi et al., 2008), and lack of Pavlovian withdrawal regarding predictions of negative outcomes may contribute to depressive pessimism and rumination (Huys and Dayan, 2009). These deficits may arise from impaired neuroplasticity in the amygdala and nucleus accumbens (Talmi et al., 2008). Unlearned, evolutionary pre-specified and inflexible responses to threat play major roles in specific phobias such as snake phobia and spider phobia (Ohman and Mineka, 2001). Because these conditions increase risk for other, more prevalent conditions including major depression, genetically determined stress responses may significantly contribute to common stress-related psychiatric conditions. Neuroeconomics-derived theoretical predictions about optimal adaptation may provide an objective metric to examine psychopathology as suboptimal behavior.

Behavioral avoidance is a diagnostic criterion of post-traumatic stress disorder and a major behavioral problem in all stress-related psychiatric disorders. The neurobiological mechanisms leading to reinforcement of avoidance are not well understood. Based on studies using dopamine antagonists, it has been proposed that it is not the reduction of the negative prediction itself but rather the dopamine-related positive outcomes of the avoidance behavior that control avoidance responses (Dayan and Seymour, 2009). The consequences of behavioral avoidance have been described as a "hot stove" effect by economists (Denrell and March, 2001). They showed that avoidance is the result of exclusively reproducing actions that led to success in the past, while neglecting potentially good alternatives based on inadequate sampling. Biased sampling may be a particularly important factor in individuals with early negative experiences such as child abuse, which is a strong predictor of psychiatric disorders. The "hot stove" effect is a possible explanation of how simple behavioral interventions such as exposure to avoided situations and increasing the general activity level represent the most effective treatments for anxiety and stress disorders. In monkeys, when the utility in a task wanes, activity in the locus coerulues-norepinphrine system induces a disengagement from the current task and an increase in exploratory behavior (Aston-Jones and Cohen, 2005). Neuroimaging research has revealed that activity of the bilateral frontal polar cortex is crucial for exploratory decision in humans (Daw et al., 2006). Interestingly, brain activity in the exploration-related frontopolar cortex was found to be increased as response to stressful aversive events such as noxious hot and cold stimulation (Becerra et al., 1999; Tracey et al., 2000), unpleasant arousing words (Maddock et al., 2003) and unfair social behavior (Sanfey et al., 2003), whereas reduced activity in this cortical region has been associated with the experience of depressive symptoms (Aalto et al., 2002; Drevets et al., 2008; Tashiro et al., 2000).

The following are our expectation-related hypotheses of psychiatric disorders:

- Deficits in model-based learning increase risk of addiction, eating and anxiety disorders.
- Dysfunctions of the orbitofrontal cortex and the amygdala are the neural substrate of model-based learning deficits.
- Deficits in Pavlovian fear conditioning and/or Pavlovian-instrumental transfer increase risk of mood and anxiety disorders.
- Deficits in Pavlovian fear conditioning is associated with impaired neuroplasticity of the amygdala, anterior insula and anterior cingulate cortex, while impaired Pavlovian-insturmental transfer is associated with abnormal function of the amylgdala and nucleus accumbens.
- A reduced rate of exploratory decisions increases the risk of post-traumatic stress disorder and depression.
- Norepinephrine deficiency and dysfunction of the frontopolar cortex is the neural substrate for reductions in exploratory behavior.

5. Uncertainty

Living in a modern, free society requires that people make a wide range of important decisions that involve considerable uncertainty, including choices about education, marriage, professional development and pension investments with important long-term consequences. Decision-making under uncertainty is one of the most complex problems in decision theory. The standard economics theory assumes that the willingness to take risks depends on the concavity of the utility function. In prospect theory, risk taking also depends on the probability weighting function (Kahneman and Tversky, 1979). Neuroeconomics approaches highlight the role of emotions in decision-making under uncertainty (Loewenstein et al., 2001). Given this complexity, it is not very surprising that many individuals fail to take optimal actions in the face of unpredictability and uncertainty in a rapidly changing world.

As mentioned above, avoidance of consumption uncertainty may represent an important risk factor in the development of domain-specific psychiatric disorders such as substance abuse and addiction. Moreover, neuroticism and harm avoidance, the strongest and most consistent personality risk factors for stress-related psychiatric disorders, could be interpreted as a negative attitude toward risk. However, this may not always be the case. Even very anxious individuals demonstrate an inclination toward risk in specific domains. For example, it is not uncommon for the same anxious individual who checks his front door one hundred times a day also enjoys risky car driving (Weber et al., 2002). A genetic epidemiological study on pathological gambling showed that the genes underlying the risk for gambling largely overlapped with the genes indicative of risk for depression (Potenza et al., 2005). As a result, it may be the pessimistic perception of the probability of uncertain outcomes, rather than abnormal risk preferences (utility transformations), that leads to uncertainty aversion in people with psychiatric conditions (Weber et al., 2002). Neuroeconomics studies have provided converging evidence for involvement of the anterior insula in the processing of uncertainty (Mohr et al., 2010). Given that increased reactivity of the anterior insula is related to the risk of a wide range of psychiatric conditions (Paulus et al., 2003), one may hypothesize that abnormal processing of uncertainty significantly contributes to stress-induced psychopathology.

In experiments using aversive events with known or learned probabilities (i.e., *predictable* aversive events), subjects with post-traumatic stress disorder and other anxiety disorders exhibit surprisingly normal threat responses (Blechert et al., 2007). However, these subjects show excessive stress responses when exposed to *unpredictable* aversive events (Grillon et al., 2009). Unpredictability activates the hippocampus (Hasler et al., 2007), and hippocampal dysfunction has been associated with hopelessness and the pathophysiology of a broad range of stress-induced psychiatric conditions (Geuze et al., 2005). Economists use the term "ambiguity" to describe situations where outcome options and/or probabilities are unknown. In 1961, Ellsberg demonstrated that people clearly distinguish between risky and ambiguous options and prefer known risk over ambiguity (Ellsberg, 1961). Ellsberg called this phenomenon ambiguity aversion. Ambiguity aversion has been observed for both losses and gains (Inukai and Takahashi, 2009), and increased ambiguity aversion may potentially lead to decreased stress tolerance and higher risk for psychopathology

(Blanchette and Richards, 2003). For example, some individuals with borderline personality disorder (BPD) cannot maintain social relationships because they develop intense abandonment fears and inappropriate anger when faced with the "normal" ambiguity that is inherent in all social relations. The black-and-white thinking of individuals with these conditions can be interpreted as an attempt to use cognition to reduce ambiguity. There is preliminary evidence that intact ambiguity-induced activation of the posterior inferior frontal sulcus is needed to implement contextual analysis and inhibit impulsive responses (Huettel et al., 2006).

The following are our uncertainty-related hypotheses of psychiatric disorders:

- The pessimistic perception of the probability of uncertain outcomes represents a risk factor for mood and anxiety disorders.
- Increased activation of the right insular cortex is the neural substrate of such pathogenetic risk assessments.
- Excessive ambiguity aversion is a risk factor for BPD.
- Dysfunctions of frontoparietal networks are underlying pathogenetic ambiguity aversion.

6. Gain–loss asymmetry

Experiments in behavioral economics have repeatedly shown that, in the context of risky choices, losses loom larger than gains by a factor of about 2:1. This implies that individuals' utility functions depend on changes in value (e.g., gains and losses relative to a reference point that may change from situation to situation) rather than the final value of wealth. The fact that most people show loss aversion implies a gain–loss asymmetry, which can be formalized by a loss function that is steeper than its corresponding gain function. Regarding decision-making under risk, this gain-loss asymmetry implies that people are rather risk averse when choosing between gains, and rather risk seeking when choosing between losses. As a consequence, framing of decisions and labeling of outcomes as gains or losses have an important influence on valuation and decision-making. In contrast to expected utility theory, *prospect theory* is a descriptive model of economic behavior that takes these psychological factors into account (Kahneman and Tversky, 1979). *Prospect theory's* value function has three essential characteristics (see Fig. 2). *Reference dependence:* the value is defined relative to a reference point. *Loss aversion:* the loss function is steeper than the gain function. *Diminishing sensitivity:* the marginal value of both gains and losses decreases with their size. As a result, the value function is assumed to be concave for gains, convex for losses, and steeper for losses than for gains. The most popular parametrization of this qualitatively described function relies on a power function (Tversky and Kahneman, 1992):

$$v(x) = \begin{cases} x^{\alpha} & x \geq 0 \\ -\lambda(-x)^{\beta} & x < 0 \end{cases}$$

where $\alpha, \beta > 0$ measure the curvature of the value function for gains and losses and λ is the coefficient of loss aversion. Experimental studies have consistently found the following median values: $\alpha = 0.88$, $\beta = 0.88$ and $\lambda = 2.25$ (Hastie and Dawes, 2001). The latter finding indicates that losses are about twice as painful as gains are pleasurable. The value function apples to riskless, risky and ambiguous choice.

Exaggerated sensitivity to loss may also represent a risk for depression, given that loss experiences are the most frequent precedent of major depressive episodes (e.g., romantic loss, loss of loved ones, job loss). This suggests that exaggerated loss aversion, possibly associated with exaggerated framing of selling highly valued objects as losses, may reduce stress tolerance. This hypothesis is supported by a neuroeconomics study demonstrating an association between right insula activity and susceptibility to the endowment effect (Knutson et al., 2008), given that increased right insular activity has been related to neuroticism and harm avoidance representing important risk factors for stress-related psychiatric conditions (Paulus et al., 2003). In addition, loss aversion is most pronounced for safety and income (Tversky and Kahneman, 1991), and loss of these goods is particularly depressogenic. Excessive loss aversion also implies excessive risk aversion with respect to negative outcomes, which may underlie the high rates of anxiety symptoms in depressed patients. Reduced sensitivity to rewards is another key feature of depression (Pizzagalli et al., 2009), which can be formalized as flattening of the gain function (excessive diminishing sensitivity to gains). Fig. 2 displays hypothetical prospect theory value functions for subjects with and without depressive vulnerability.

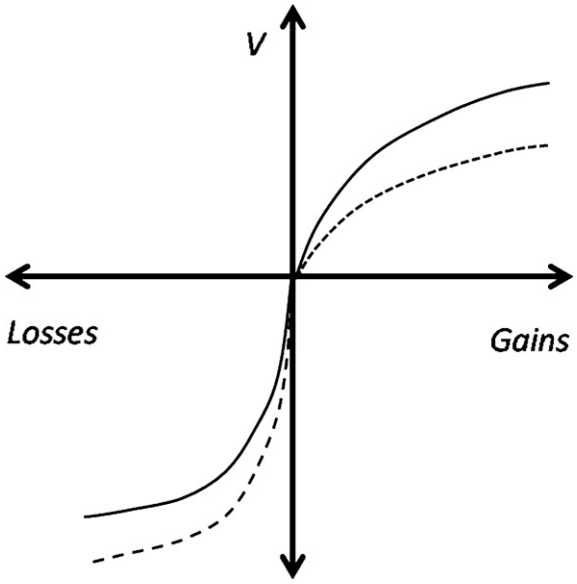

Fig. 2. Hypothetical utility functions from prospect theory in subjects with and without risk for depression. The solid line represents a hypothetical prospect theory value function in subjects without depressive vulnerability. The dashed line represents a hypothetical value function in subjects at risk of depression with hyposensitivity to gains and hypersensitivity to losses.

A behavioral economics study examined *prospect theory's* value function in asymptomatic individuals with a history bipolar disorder (Chandler et al., 2009). This study demonstrated that individuals at risk for bipolar disorder were less sensitive to framing effects than were healthy controls: these individuals made more risky choices for increased gains and made fewer risky choices to avoid losses than did controls. These results suggest that bipolar disorder is not associated with a generalized tendency to risk-taking (Najt et al., 2007) but with a reduced sensitivity to psychological factors that inhibit or enhance risky behavior involving outcomes of value. The authors of this interesting study hypothesized that both loss and gain functions are steeper in bipolar individuals than in unaffected people. Regarding the loss function, this implies excessive loss aversion and risk aversion in response to dilemmas involving negative outcomes. This is consistent with our loss aversion hypothesis of unipolar depression, possibly explaining the high prevalence of depressive and anxiety symptoms in bipolar individuals. The relatively steep gain function would make the selection of risky behaviors associated with large rewards more tempting, possibly explaining impulsivity and risk-seeking in bipolar disorder. The hypothesis that bipolar individuals have less *diminishing sensitivity* to increasing gains, resulting in a steeper relationship between rewards and their subjective values, could explain bipolar patients' excessive

preoccupation with rewarding experiences (Chandler et al., 2009). Together, this value function hypothesis by Chandler et al. has the potential to elucidate the mechanisms underlying the co-occurrence of heterogeneous symptom clusters such as excessive risky taking and anxiety/depression in bipolar disorder.

The following are our gain–loss asymmetry hypotheses of psychiatric disorders:

- Excessive loss aversion increases stress sensitivity, particularly to the experience of losses.
- The neural substrate of the potentially pathogenetic hypersensitivity to losses includes hyperactivity of the amygdala and the right anterior insula.
- Reduced diminishing sensitivity to increasing losses and increasing gains is a risk factor for bipolar disorder.

7. Social preferences

Historically, people were sequestered in "lunatic asylums" when they did not comply with social norms. Although current diagnostic methods in psychiatry are based on symptoms and not on social norms, social functioning continues to be a key criterion in the classification of a symptom as pathological. All types of psychological treatments for psychiatric problems directly or indirectly address problems with social adjustment, and interpersonal psychotherapy is effective even in reducing psychiatric symptoms that are not primarily social in nature (Fairburn et al., 1995).

Economists have formalized the notion of preference (i.e. relative value) to describe the choices that people make regarding trade-offs between different categories of goods. Social preferences, recently introduced from behavioral economics (Fehr and Schmidt, 1999a), expand this concept to reflect the fact that people value the well-being of other individuals. More formally, social preferences describe behavior or motives with respect to an individual's positive or negative feelings about others' material payoffs. Formalized social preferences include self-interest, altruism, reciprocity, inequity aversion and betrayal aversion, and all have an important effect on social cooperation (Camerer and Fehr, 2002).

There is increasing evidence that complex social emotions such as trust, shame, guilt and envy play important roles in choices related to social preferences. Based on game theory, economists have developed social experiments to elicit specific social preferences. For example, inequity aversion in a two-player game can be formalized as follows (Fehr and Schmidt, 1999b):

$$U_i = x_i - \alpha_i(x_j - x_i,), \text{ if } j \text{ is better of than } i$$
$$U_i = x_i - \beta_i(x_i - x_j), \text{ if } i \text{ is better off than } j$$

where U_i is the utility of player i, x_i the payoff of player i, and x_j is the payoff to player j. α_i measures the disutility from being worse off (envy), and β_i measures the disutility from being better off (compassion, feeling of guilt). Experiments to measure social preferences involve real monetary stakes and real interaction partners. Repeated play among the same players is typically excluded to control for important confounds such as reputation and punishment. Because experiments measuring social preferences are safe, do not involve psychological stress and can be combined with neuroimaging, neuro-stimulation and pharmacological manipulations, they are advantageous for research in psychiatric populations.

The human response to social inequity can involve strong emotions, and dysfunctional emotional responses to inequity are used as diagnostic criteria in official psychiatric classification schemes (First et al., 2001). Fox example, excessive guilt, which reflects advantageous inequity aversion, is a diagnostic criterion of major depressive disorder, and excessive envy, which reflects disadvantageous inequity aversion, is a diagnostic criterion of narcissistic personality disorder. Neuroeconomic research has demonstrated that the brain has a strong sensitivity to social equity considerations. This sensitivity is particularly evident in the striatum and the ventromedial prefrontal cortex (Tricomi et al., 2010), which have appeared to be key brain regions in the pathophysiology of affective and personality disorders. Together, these observations indicate that social emotions may lie at the core of psychiatric disorders, and a quantitative measure of their dysfunction via neuroeconomic tools may provide improved diagnostic accuracy.

In the ultimatum game (Güth et al., 1982), the tension between economic self-interest on the one hand and reciprocity and equity considerations on the other hand can be captured. In this game, two anonymous players, a proposer and a recipient, must agree on the division of a given amount of money. The proposer can make one single suggestion on how to allocate between the two by offering a certain amount to the recipient. The recipient can reject the proposed allocation. If she rejects it, both players receive nothing. Rejection has been conceptualized as the inhibition of a selfish impulse in the limbic region of the brain by the right dorsolateral prefrontal cortex in favor of pro-social motives such as negative reciprocity, altruistic punishment or inequity aversion (Knoch et al., 2006). Neuroeconomics research has demonstrated that risk factors for depressive disorders such as sad mood and serotonin deficiency is associated with an exaggerated emotional response to unfair offers and an increased rejection rate in the ultimatum game (Crockett et al., 2008; Harle and Sanfey, 2007). This suggests that high levels of equity considerations represent a risk for mood disorders. It is noteworthy that in the private impunity game certain players reject unfair offers even when this behavior increases rather than decreases inequity. It has been proposed that this behavior is a by-product of emotion (Takagishi et al., 2009a; van't Wout et al., 2006), typically anger or moral disgust, to preserve moral integrity (Yamagishi et al., 2009). Imaging data revealed that this emotional response is paralleled by activation of the right anterior insula (Takagishi et al., 2009b), which has been found to be hyperactive in subjects scoring high on neuroticism (Paulus et al., 2003).

Trust may be a particularly important concept for psychiatry given that trust permeates family relations, friendship relations and professional relations, including the doctor-patient relationship (Fehr, 2009). A trusting therapeutic alliance is one the strongest predictors of success in most psychotherapies (Orlinsky et al., 2004). In a trust game, two players are each given an initial endowment. The first player then decides whether to keep her endowment or send all or part of it to the second player, which reflects trust. The experimenter doubles or triples the transferred money received by the second player, which reflects the fact that most social exchanges are profitable. The second player then decides whether to keep the amount received or send some of it back to the fist player, which indicates trustworthiness. The second player profits most if she keeps all the transferred money; however, if the first player anticipates this behavior, she will not transfer his endowment, thus excluding the chance for mutual gain. Psychologically healthy first players invest an average of half of their endowment with second players, and healthy second players repay on average as much as the first player invested (Camerer and Fehr, 2002). Interestingly, first players have been found to invest less with second players than they do in other risky choices with non-social random outcomes, indicating a pure aversion to social betrayal (Bohnet and Zeckhauser, 2004). A clinical study demonstrated that, as first players, patients diagnosed of BPD transferred smaller amounts than did healthy controls (Unoka et al., 2009). BPD patients' normal performance in a non-social risk game suggest that these individuals may have a particular deficit in social trust as opposed to a dysfunction in general risk calculation or attitudes. "Partner matching" games that involve repeated play between the same

two players have been used to study behavior relevant to maintaining interpersonal relationships such as reputation formation and the repair of relationship disruption. Using a repeated trust game, a neuroeconomics study investigated interpersonal relationship problems in subjects with BPD (King-Casas et al., 2008). In the experiment, BPD subjects showed a striking inability to maintain cooperation relative to healthy controls. This inability was associated with a lack of response of the anterior insula to reduced offers received from the partner, indicating a potential rupture of social cooperation. This may have inhibited BPD subjects from responding adequately and repairing trust and cooperation. This study is perhaps the best example of the potential of the game-theoretic approach to elucidate the bio-psycho-social interplay underlying complex psychopathology. Other game theory studies have also been useful in uncovering underlying mechanisms in other psychiatric disorders. For example, patients with high-functioning autism and individuals with generalized social anxiety disorder showed reduced neural activation in the medial prefrontal cortex while interacting with human partners in trust games (Chiu et al., 2008; Sripada et al., 2009). Although impaired trust has been implicated in many psychiatric disorders, this impairment may be amenable to specific treatments. Infusion of the synthetic neuropeptide oxytocin intranasally reduced fear of betrayal in a trust game paralleled by dampening of amygdala activity in response to social signals (Baumgartner et al., 2008).

Most evolutionary theories of affective disorders are related to the social function of emotions. Depressive states, for example, represent a psycho-biological response pattern that is part of the inherited behavioral repertory of humans (Allen and Badcock, 2003; Gilbert, 2006; Price et al., 1994). This infers that mild depression had some useful function over the course of human development, and that those ancestors who had the capacity to become depressed had an evolutionary advantage over those without this capacity. Clinical depression may be a pathology of this otherwise adaptive response (Allen and Badcock, 2003). There is strong epidemiological evidence suggesting that psychopathology-inducing stressors are predominantly social in nature (Hasler, 2010). Social stressors have unique characteristics that are ingrained in social interactions and which influence the dynamic creation of social roles. The dominating social evolutionary theory of depression is the social competition hypothesis (Price et al., 1994). It posits that depression has evolved in relation to social competition because the depressive state contributes to a de-escalation of hierarchy conflicts. Specifically, it signals to others that the individual poses no threat, it prevents the individual from retaliating against others (anhedonia, inhibited aggression), and it helps the individual to accept an inferior social rank (low self-esteem). Although this hypothesis explains many features of clinical depression and has attracted considerable interest in the field of evolutionary psychiatry, it has yet to be tested empirically. Thanks to social decision theory, methods are now available for experimental social psychiatry to emerge as a vibrant field of study. The hawk-dove game, the battle of the sexes game and other social rank games seem well-suited to investigate the role of depressive states in social competition and cooperation at the behavioral and neurobiological levels.

The following are our social preference hypotheses of psychiatric disorders:

- Excessive inequity aversion is a risk factor for mood disorders.
- Hyperactivity of the right anterior insula and the medial prefrontal cortex, and serotonin deficiency are the neural substrate of excessive inequity aversion.
- Excessive betrayal aversion is a risk factor for borderline personality disorder and social anxiety disorders.
- Dysfunctions of the medial prefrontal cortex, hyperactivity of the amygdala and deficiency of pro-social neuropeptides are the neural substrate of excessive betrayal aversion.
- Excessive social competition aversion is a risk factor of depression.

8. Time preferences

Intertemporal choices involve trade-offs among costs and benefits that occur at different times. Such decisions are ubiquitous. Adam Smith realized the importance of intertemporal choices for the Wealth of Nations, and their importance in the determination of individual health and well-being is undeniable.

There are two major genetic factors (sets of risk genes) underlying non-psychotic psychiatric disorders that are related to self-control and possibly to intertemporal choice. One factor increases the risk of internalizing disorders, i.e., unipolar depression and anxiety disorders, which are characterized through internal problem-solving, overinhibition and overcontrol (Hettema et al., 2006b), possibly associated with excessive future-orientation. The other factor increases the risk of externalizing disorders including anti-social personality disorder, alcohol and drug dependence that accompany outward directed behaviors, aggression, lack of control and present-orientation (Hicks et al., 2004). The internalizing factor has been associated with genes of the serotonergic and GABAergic neurotransmitter systems, such as the serotonin transporter gene (Lesch et al., 1996) and the gene of the GABA-synthesizing enzyme glutamic acid decarboxylase 1 (Hettema et al., 2006a). The externalizing factor has been associated with the gene encoding the neurotransmitter-metabolizing enzyme monoamine oxidase A (Caspi et al., 2002).

On Albrecht Dürer's engraving "Melancolia I" (Fig. 3), the depressed, frustrated mood of a female figure is associated with a half-empty hourglass, implying the running out of time, which is a frequent concern of patients with the inability to experience immediate rewards. Anhedonia, an important risk factor and endophenotype of depression (Hasler et al., 2004), has been associated with decreased delay discounting, i.e., less devaluation of rewards as a function of delay (Lempert and Pizzagalli, 2010). Even patients experiencing an acute depressive state, hypersensitivity to negative outcomes in the extremely distant future was demonstrated (Takahashi et al., 2008b); however, their immediate actions were more myopic, possibly reflecting the increased visceral influence engendered by the acute stress response (Takahashi, 2004; Takahashi et al., 2007, 2008a, 2010). Future-orientation in depression is potentially adaptive, as it has been found to predict low suicide risk in depressed patients (Hirsch et al., 2006). One evolutionary advantage of anhedonia may have been its facilitation of future-orientation. Abraham Lincoln is a striking example of a person with severe deficits in the ability to experience immediate rewards, causing him almost unbearable anhedonia and disgust (Shenk, 2006). Ironically, his extreme farsightedness has assured his admirable position in political history. Excessive farsightedness, however, is likely pathogenetic in hoarding disorder. Hoarders are unable to throw items away because of the potential, however unlikely, that the item will be useful in the future. Because of their extreme future orientation, pathological hoarders usually neglect the present situation, often leading to conflicts with spouses and landlords.

The neuroeconomics study of inter-temporal choice in psychiatric populations has the potential to elucidate the neurobiological underpinnings of abnormal time preferences associated with psychopathology. Behavioral economists have begun to conceptualize externalizing psychiatric problems such as addiction and impulsivity with respect to time preferences. Becker and Murphy

Fig. 3. Albrecht Dürer's engraving "Melancolia I". The depressed, frustrated mood of a female figure is associated with a half-empty hourglass, implying the running out of time, which is a frequent concern of patients with the inability to experience immediate rewards. Future-orientation seems to be an adaptive response to this inability.

(1988) developed an intriguing model to explain addiction through rational choice, by assuming that individuals maximize utility consistently over time. Their model understands addiction as an interaction between a person and a good, and predicts that people who heavily discount the future are at risk of addiction. In support of this, increased delay discounting has been found to be a predictor of future nicotine consumption (Audrain-McGovern et al., 2009), and delay discounting of *gains* has been related to frequency and dosage of nicotine self-administration (Ohmura et al., 2005). The Becker and Murphy utility model explains a wide range of clinical characteristics including the relationship between present-orientation and addiction, the unstable consumption of the addictive good, the increasing myopia experienced by addicts, the role of stress on consumption, and the need for abrupt withdrawal in the treatment of addiction. The predictions regarding the stress-addiction association is consistent with the effects of stress hormones on time-discount rates (Takahashi, 2004; Takahashi et al., 2007, 2008a, 2010). The predictions regarding the characteristics of the addictive good is consistent with the pharmacological properties of addictive chemicals, and the model explains why many addicts have a strong need for the addictive good without enjoying any positive benefits from its consumption. Compared to behavioral models of addiction that are frequently used in psychiatry, the Becker and Murphy model has the advantage of making mathematically precise predictions about the influence of numerous interacting pharmacological, social and psychological factors related to addiction. This is crucial since interactions among these factors are thought to underlie the pathogenesis of psychiatric conditions.

In domain-specific externalizing disorders such as addiction and bulimia nervosa, anomalies of time preferences may be domain-specific, a phenomenon that is difficult to model using standard economic theory. In a recent neuroeconomic study in women at risk for bulimia, time and risk preferences with respect to pecuniary incentives appeared to be normal, and dopamine depletion exclusively induced eating disorder symptoms without inducing any other psychiatric symptoms or changes in non-food preferences (Grob et al., in preparation). Personality research has similarly failed to find strong and consistent risk factors for domain-specific externalizing disorders. For example, the risk of drug addiction appeared to be unrelated to impulsivity (Swendsen et al., 2002), impulsive alcohol consumption did not increase the risk for alcohol dependence (Slutske, 2005), and cocaine addicts can be more prudent when investing in the stock market than the average person of the general population (Weber et al., 2002). These findings call into question the validity of a simple explanation of psychopathology through weak wills, temptation and myopia. In psychiatric research it is important to find explanations for the disease risk; correlates of acute symptoms may not be informative because acute states of distress can make people weak, tempted and myopic irrespective of disease causation.

Two major models of temporal discounting have been proposed to mathematically describe the temporal discounting of future events (Green and Myerson, 1996). The exponential discounting model has the form:

$$V = Ae^{-kD}$$

where V is the present, discounted value of a reward A available after a delay of D units of time. Economists usually favor this model where valuation falls by a constant factor per unit delay, regardless of the total length of the delay. However, empirical research in both animals and humans has shown that a hyperbolic time discounting function tends to fit experimental data better than the standard assumption of an exponentially decreasing discount factor. The general hyperbolic time discounting function has the form:

$$V = \frac{A}{(1 + kD)^s}$$

where k and s are free parameters, and V, A and D have the same meaning as in the exponential model. The simple hyperbolic time discounting function is a special case of the general hyperbolic function when $s = 1$. This means that valuations fall very rapidly for small delay periods followed by a more gradual declining continuing for longer delay periods. Hyperbolic time discounting creates a time inconsistency ("preference reversal") in intertemporal choice. There is preliminary empirical evidence that an error in time perception following the Weber-Fechner law might underlie this preference reversal (Zauberman et al., 2009). Theoretically, if time is scaled into a logarithmic internal representation, rather than a linear representation, then even when individuals try to discount delayed rewards exponentially, their actual discounting may follow the hyperbolic function (Takahashi, 2005). The most striking effect of this inconsistency is an "immediacy effect": discounting becomes dramatic when one delays consumption that would otherwise be immediate (Prelec and Loewenstein, 1991). Whether or not this taste for immediate gratification relates to impulsive psychopathology remains to be determined (McLeish and Oxoby, 2007).

While standard decision theory is well equipped to predict decision-making in "cool" settings, it has difficulty explaining situation- and reward-specific decisions at the "hot" end of the spectrum. Addressing this limitation, Loewenstein has introduced the concept of *visceral factors* to explain impulsive behaviors such as sexual misconduct, overeating, substance abuse and crimes of

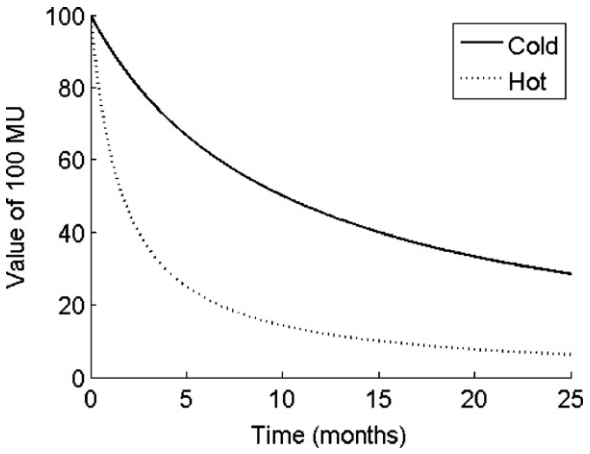

Fig. 4. Hypothetical temporal discounting functions are plotted for "hot", emotional and impulsive states and for "cold", non-aroused states. MU = monetary unit. Figure was constructed by Jan Engelmann.

passion that are frequently at odds with long-term self-interests (Loewenstein, 1996). Visceral factors have a direct hedonic impact and influence the relative desirability of different goods and actions. These factors change rapidly and predictably correlate with external circumstances. The present-orientation induced by visceral factors applies only to goods that are associated with them without changing the individual's permanent behavioral disposition. In addition, visceral factors can "crowd out" other motivational factors, possibly explaining the reduced responsiveness of the reward system to non-drug related cues in addicted individuals (Loewenstein, 1999). People usually underestimate the impact of visceral factors in the future, which is evident in relapse behavior of addicts who are convinced that they can indulge in low levels of consumption without relapsing (see Fig. 4: "hot" discounting function). The concept of visceral factors is consistent with studies on time preferences in drug addicts showing stress-induced and drug-craving induced increases in delay discounting (Giordano et al., 2002; Takahashi et al., 2008a). In summary, the concept of visceral factors has the potential to explain excessively present-oriented self-damaging behaviors associated with psychiatric disorders that are difficult to explain by standard decision theory alone. In an alternative view, delay discounting arises from the existence of multiple valuation systems in the brain (Dayan et al., 2006). In particular discounting follows when a hard-wired Pavlovian approach of proximal rewards dominates over goal directed action.

Neuroeconomic research findings implicate the dopaminergic system and brain regions associated with timing processes, including the frontal cortex, basal ganglia and cerebellum, in encoding discounted utility (Kable and Glimcher, 2007; Pine et al., 2010). A molecular neuroimaging study in individuals addicted to cocaine demonstrated that drug cravings were associated with increased release of intrasynaptic dopamine in the striatum (Wong et al., 2006). Timing abnormalities in attention-deficit hyperactivity disorder has been related to dopamine dysregulation, and the dopamine reuptake inhibitor mehtylphenidate seem to normalize such temporal processes (Rubia et al., 2009). Secondary impulsiveness associated with an impaired timing function has been described in patients with frontostriatal brain regions (Bechara and Van Der Linden, 2005). Reduced striatal reactivity to rewards may be the neural substrate of future-orientation associated with anhedonia (Pizzagalli et al., 2009).

The following are our time preference hypotheses of psychiatric disorders:

- Excessive present-orientation represents an important risk factor for impulse control-related psychopathology including impulsive personalities, substance abuse, attention-deficit hyperactivity disorder, mania, and impulsiveness in psychoorganic syndromes.
- Excessive future-orientation represents a risk factor for specific psychiatric disorders such as hoarding.
- Impairments in the brain's timing function and dysregulation of visceral factors are important psychological explanations of pathogenetic time preferences.
- The neural substrate of pathogenetic time preferences includes dopamine dysregulaton, and structural and/or functional abnormalities in frontostriatal and frontocerebellar timing systems.

9. Revealed and real preferences

Economists assume that people attempt to choose the highest valued goods that they can afford, and that their revealed preferences reflect their real preferences. Because individuals with psychiatric conditions often reveal preferences that seem not to reflect true preferences (e.g. they seem not to maximize their long-term utility), it is tempting to consider psychiatric patients as irrational people whose revealed preferences are dissociated from their real preferences. While cognitive errors have been proposed to explain irrational behaviors, this explanation may not specifically relate to psychiatric disorders given empirical evidence that the absence of common cognitive errors (Alloy and Abramson, 1979; Chandler et al., 2009; Harle et al., 2010) and higher than average IQ (MacCabe et al., 2010) may represent a risk for becoming mentally ill. More sophisticated explanations of irrational behavior include multiple-self models, which have been independently developed in psychiatry and behavioral economics. The term 'schizophrenia' (split mind) is a remainder of this type of theory in psychiatry. In economics, multiple-self models have been used to explain inconsistent time preferences (Schelling, 1984). While such models are intuitively appealing, they fail to specify why a specific self emerges, and have yet to be used to derive testable implications.

Findings from genetic epidemiology argue against irrational decision-making as the predominant cause of psychiatric disorders. Psychiatric disorders are very common up to 50% of the general population has at least one psychiatric disorder in their lifetime (Kessler et al., 2005). In addition, common genetic variants and not genetic errors (mutations) are thought to underlie common psychiatric disorders, and there is typically no point of rarity in the distribution of psychiatric symptoms that can differentiate pathological from non-pathological states. Finally, the early age of onset of psychiatric disorders negatively impacts reproduction, raising the question of why the forces of evolution have not eliminated the genes that increase the risk of irrational decision-making. Why would evolution produce so much irrationality? In fact, there is preliminary evidence that the frequency of genetic variants associated with mood and anxiety disorders, e.g., the s-allele of the serotonin transporter gene, increased rather than decreased in the development of the human species (Lesch et al., 1997), suggesting an adaptive advantage of mild psychiatric symptoms (Nesse, 2000). While evolution has its limitation (i.e., optimal adaptation is not achieved in each individual), who would claim that Abraham Lincoln, Winston Churchill and Ernest Hemingway were not able to maximize utility despite suffering from severe psychiatric conditions? Irrational decision-making may, however, explain abnormal choices in severe neurodevelopment disorders such as certain types of autism and schizophrenia that are caused by structural genetic alterations (Karayiorgou et al., 2010). Interestingly, self-reported well-being by people with these severe conditions is typically higher than well-being reported by subjects with less severe psychiatric disorders (Priebe et al., 2010), possibly because

of the capacity of these individuals to permanently distort reality perception.

Preferences associated with psychiatric disorders may represent real preferences. A patient who began drinking alcohol to cope with a series of abusive relationships, thereby focusing on a reward with high availability and predictable risks, may indeed have revealed a real preference by choosing alcohol dependence instead of committing to the risks of new, potentially abusive relationships. A dependence on alcohol seems to be particular rational in present-oriented individuals with relatively low alcohol-related costs, e.g., in healthy elderly individuals (Becker and Murphy, 1988). The psychiatric terms "rational suicide" or "balance suicide" refer to the possibility that even committing suicide may sometimes reflect a true preference, although this a matter of debate. One may object that cocaine use in young adults cannot be rational, given the generally available information about the rapid hedonic downward spiral of cocaine use (Loewenstein, 1996). However, only 5–6% of recent-onset cocaine users become cocaine abusers (O'Brien and Anthony, 2005). Thus, it is indeed difficult to predict the risks associated with cocaine use at an individual level.

The learned helplessness model of depressive withdrawal (Seligman, 1972) is an example of dissociation of real and revealed preferences in the absence of irrational choice. The main finding is that animals that were exposed to uncontrollable stressors (e.g., electric shocks in a closed cage) do not escape a subsequent similar, but escapable situation (e.g., electric shocks in an open cage). That animals chose to give up trying to escape is maladaptive in learned helplessness experiments, but nevertheless adaptive in many natural situations where potential pay-offs from investments are low (Nesse, 2000). That animals fail to escape when it is possible seems to confirm that subjects are not fully knowledgeable of relevant information when making decisions (Stigler, 1961). The fact that some animals do escape suggests that genetic factors and early experiences influence decision making under uncertainty. Risk of psychiatric disorders may result from a mismatch between these factors and the pay-off probabilities of the present environment.

There is a practical need to differentiate pathological from "real", i.e., healthy, preferences when treating patients suffering from psychiatric disorders. Freud asserted that winning honor, power, wealth, fame and the love of women were men's real preferences (Freud, 1910). Such a concrete concept of true preferences enables psycho-analysts to interpret a particular valuation or choice as a reflection of a real desire, or the sublimation or the perversion of a real desire. Given its questionable generalizability, Freud's value concept has turned out to be overly simplistic and it is no longer widely accepted in modern psychiatry. Economists' more abstract concept of utility may serve as a new framework from which to evaluate choices made by individuals suffering from psychiatric disturbances on an individual basis. The Cognitive Behavioral Analysis System of Psychotherapy is a novel and effective psychotherapeutic approach for chronic depression (Keller et al., 2000) and implicitly applies such a framework. In 'situational analyses,' therapist and client jointly analyze a specific situation regarding the revealed outcome compared to the desired outcome. The insight into suboptimal utility maximization is the key motivational force in this treatment. Neuroeconomic approaches have the potential to test the hypothesis that reflection about utility maximization can lead to enhanced influence of higher-order motivational factors such as long-term well-being and improved health. The influence of these motivational resiliency factors on decision-making has been associated with activity in specific regions of the lateral frontotemporal cortex (Hare et al., 2009). Interestingly, abnormal activity in these brain regions (bilateral prefrontal gyrus, right superior temporal cortex) has been associated with harm avoidance and negative emotion (Aalto et al., 2002; Sugiura et al., 2000); degeneration of these brain regions, for example in frontotemporal dementia, can lead to psychiatric problems such as social disinhibition, lethargy, pathological gambling and dysregulation of food intake (Piguet et al., 2011).

The following are our rationality-related hypotheses of psychiatric disorders:

- Psychopathology can reflect decision-making errors, suboptimal utility maximization or rational choice.
- Social risk factors play a particularly important role in "rational" psychopathology.
- Dysregulaton of the inferior frontal gyrus, the precentral gyrus and the superior temporal gyrus is the neural substrate of psychiatric problems related to deficits in higher-order motivational factors.

10. Normative models of dopamine neurotransmission

In 1957 dopamine was identified as a neurotransmitter, and the discovery that the dopamine system was the primary site of action of antipsychotic drugs was a crucial step toward neurobiological models of mental disorders. Although the one-neurotransmitter-one-disease paradigms have been abandoned, the neurotransmitter hypotheses of psychiatric disorders are still quite simple. Increased dopamine activity is thought to play a major role in schizophrenia because the therapeutic effects of almost all antipsychotics strongly correlate with antagonism at dopamine D2 receptors, and because dopamine releasing drugs worsen schizophrenia symptoms (Howes and Kapur, 2009). The monoamine-deficiency hypothesis posits that depletion of the central neurotransmitters serotonin, norepinephrine and dopamine is the biological basis of depression. Dopamine-deficiency has been implicated in a wide range of other pathological conditions such as addiction, anxiety disorders, attention-deficit/hyperactivity disorder, compulsive gambling and obesity.

Normative models of neurotransmission may considerably improve neurotransmitter theories of psychiatric conditions. Neuroeconomists have successfully used normative or near-normative models to interpret the function of the neurotransmitter dopamine (Montague et al., 1996). The midbrain dopamine neurons show homogenous, phasic activation to unpredicted rewards, monotonically increasing with reward magnitude (Tobler et al., 2005), suggesting that dopamine codes for reward value or utility. Since dopamine activity as response to rewards codes a prediction error irrespective of specific combinations of reward magnitude and probability (Fiorillo et al., 2003), it seems to implement the crucial term of the Rescorla-Wagner temporal difference reinforcement learning model. Given evidence that reward learning is impaired in a wide range of psychiatric conditions (Grob et al., in preparation; Nestler and Carlezon, 2006), applying normative models of dopamine to describe such impairments will help to interpret aberrant behavior in the context of molecular neuroimaging.

Risk is an important factor in reward learning. When expecting to make large prediction errors, one's learning rate should be low (Preuschoff and Bossaerts, 2007). As a result, risk-encoding is crucial for optimal learning and may reflect risk preferences of decision makers. To incorporate prediction risk, the dopamine error teaching signal is normalized to the standard deviation. While brain regions such as the insula and the anterior cingulate cortex have been found to be activated during coding of risks (Preuschoff et al., 2008), more research is needed to fully understand the molecular basis of risk preferences and ambiguity aversion from a normative perspective. Such research will provide psychiatry with powerful tools to study maladaptive attitudes toward risk and ambiguity.

Motivation is a neuroeconomics measure of how hard an individual works to retrieve a reward. Dopamine has appeared to

code for work-related costs. Operant concurrent choice tasks offer rats the choice between lever pressing to obtain a preferred food (high work-related costs), versus consuming a less preferred food without the effort of lever pressing (low work-related costs). Experimental dopamine depletion in the nucleus accumbens specifically decreased efforts to obtain the preferred food without changing food preference in free-feeding choice tests (Salamone and Correa, 2009). Such choice paradigms are ripe for application in psychiatry to study the role of dopamine in motivation disorders such as mania and depression.

Reinforcing effects of addictive drugs are associated with large and rapid increases in extracellular dopamine (Volkow et al., 2009). In healthy humans, striatal dopamine release correlates positively with the hedonic response to drugs of abuse (Drevets et al., 2001). The rational choice model of addiction by Becker and Murphy predicts that an individual is addicted to a good only when the consumption of the good raises its marginal utility, and that higher consumption of the addictive good lowers the present utility from the same consumption level (Becker and Murphy, 1988). The predicted dynamic is consistent with the dissociation of "wanting" (marginal utility) and "liking" (utility level) of the addictive good observed in addicts. This model seems to explain the molecular pathophysiology of addictive behaviors. For example, a small group of Parkinson's disease (PD) patients compulsively overuse dopaminergic drugs such as levodopa despite harmful social and medical consequences. A molecular imaging study revealed that these PD patients exhibited enhanced levodopa-induced striatal dopamine release compared with non-addicted PD patients, and enhanced drug-induced dopamine release correlated with self-reported drug "wanting" but not "liking" (Evans et al., 2006). This example illustrates the potential of normative decision theory to elucidate the pathogenesis of neurotransmitter dysfunctions underlying psychiatric problems.

11. Conclusion

There is strong evidence that decision theory in combination with neuroscience has the potential to study and characterize important aspects of psychiatric disorders, particularly in individuals displaying normal intelligence and intact reality testing. Economic decision theory has the capacity to study a broad range of interacting factors in the same model with regard to motivational forces in humans. This appears to fit well with the needs in psychiatry, given evidence that the interplay of social, psychological and biological factors underlie psychopathology.

Table 1 provides a summary of the hypothetical relationships between neuroeconomic parameters, psychiatric disorders, associated brain regions and neurotransmitter dysfunctions. These hypotheses should be addressed in future studies. Specifically, the use of behavioral experiments based on economic decision theory in high-risk populations (e.g., healthy children of parents suffering from bipolar disorder) is encouraged to test relationships between neuroeconomic parameters and risk of specific psychiatric conditions. In addition, the temporal stability of economic

Table 1
Hypothetical relationships between parameters in neuroeconomic theory and psychiatric disorders.

Neuroeconomic parameter	Psychiatric disorders	Behavioral correlate	Associated brain regions	Associated neurotransmitter theory
Excessive loss aversion (high coefficient λ in prospect theory's value function)	Stress-related disorders (depression, non-phobic anxiety disorders)	Excessive stress response to loss experiences	Amygdala, right anterior insula (hyperactivity)	Serotonin deficiency, GABAergic deficit
Reduced diminishing sensitivity to increasing gains and losses (α and β in prospect theory's values function close to 1)	Bipolar disorder	Excessive preoccupation with rewarding experiences; loss anxiety	Striatum, orbitofrontal cortex	Complex dopamine dysregulation
Excessive present-orientation (high k in hyperbolic time discounting function)	Substance abuse and dependence, mania, attention-deficit hyperactivity disorder	Immediacy effect, myopia	Striatum, ventral prefrontal cortex, cerebellum	Excessive intrasynaptic dopamine release
Excessive betrayal aversion (difference in transferred money between trust game and non-social risk game)[a]	Social anxiety disorder, autism	Fear of social betrayal	Medial prefrontal cortex, amygdala (hyperactivity)	Deficiency of pro-social neuropeptides
Excessive advantageous inequity aversion (high β in the Fehr-Schmidt social utility function)	Depression	Excessive or inappropriate guilt	Medial prefrontal cortex, insula (hyperactivity)	Serotonin and/or norepinephrine deficiency
Exaggerated valuation of costs (shift in cost-benefit analysis)	Depression	Reductions in goal-directed behavior	Ventromedial prefrontal cortex	Tonic dopamine deficiency
Overestimation of probabilities of negative outcomes (expected utility function)	Anxiety disorders, depression	Anxious avoidance	Anterior insular cortex (hyperactivity)	Serotonin deficiency
Low marginal rate of substitution for pathogenetic goods	Substance dependence, eating disorders	Resistance to substitution of problematic behavior	Mesolimbic system, orbitofrontal cortex, amygdala	Neuroplastic deficits in dopamine-glutamate interactions
Impaired model-based learning	Obsessive-compulsive disorder, eating disorders, substance dependence	Excessive reliance on habit learning	Orbitofrontal cortex, basolateral complex of the amygdala	Dysregulation of glutamate, GABA, acetylcholine and/or monoamines
Low rate of exploratory decisions	Post-traumatic stress disorder, depression	"Hot stove" effect	Frontal polar cortex, intraparietal sulcus	Norepinephrine deficiency

[a] A more accurate formalization is based on the minimal acceptance rate (MAP) reflecting the minimum percentage of trustees who need to choose the trustworthy action to induce the investor to trust. Betrayal aversion is defined as the difference between the MAP in the trust game and the MAP in the risky dictator game (Bohnet et al., 2008).

primitives such as time and social preferences, as well as their neural underpinnings, should be studied longitudinally to evaluate their applicability as phenotypes in genetic studies. A study on the three-month stability of temporal discounting measures suggests that these measures are stable enough to predict future behaviors such as substance abuse (Ohmura et al., 2006). Family and twin studies will be necessary to examine the familiarity and heritability of economic preferences and their neural underpinnings. There is preliminary evidence that genetic factors explain approximately 40–50% of the inter-individual variance in neuroeconomics measures (Cesarini et al., 2008; Matthews et al., 2007; Wallace et al., 2007). Genetic association studies are needed to identify specific genes associated with heritable neuroeconomic markers. Because emotionally "hot" decision-making is usually more abnormal than "cold" decision-making in psychiatric conditions (Roiser et al., 2009), decision theory should be expanded toward the "hot" spectrum to increase its potential utility for psychiatric research. As we have alluded, one way to understand this is by positing multiple valuation and action systems in the brain (Dayan et al., 2006). The neuroeconomic study of natural rewards and punishments is needed to elucidate domain-specific psychiatric disorders. Studies on the effects of pharmacological manipulations including tryptophan depletion, catecholamine depletion and dopaminergic agonists on economic behavior will be needed to elucidate the relationships between neuroeconomic parameters and neurotransmitter function. Such research will provide psychiatry with computationally principled biomarkers that may prove useful as psychiatric endophenotypes. Because neuroeconomic experiments usually possess concrete concepts of optimal behavior, they allow description of psychopathology as deviation from optimal. In sum, a decision-theoretic perspective promises to clarify characterization of the motivational forces that increase risk of psychiatric disorders and explain acute psychiatric symptoms. It also offers new and exciting avenues for psychiatric neuroscience and the development of novel diagnostics and psycho-, socio- and pharmaco-therapies.

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