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Toward an Understanding of Decision Making in Severe Mental Illness

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A commonality of patients with major psychiatric disorders is their propensity to make poor decisions, which is intimately related to poor real-life outcomes. **We reviewed the literature** *on decision making as applied to severe psychiatric disorders, with particular focus* **on advances in cognitive neuroscience**. *Deficits in reward sensitivity, avoidance learning, and temporal discounting are reported in depression. Besides abnormalities in hedonic capacity, other cognitive distortions required for flexible control of behavior occur in patients with bipolar disorder and schizophrenia. A conceptual framework of abnormal decision making in mental illness could generate targeted interventions to improve quality of life and clinical outcomes.*

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In this paper, a theoretical reconceptualization of some of the critical characteristics of severe mental illness is presented as an extension of previous conceptualizations that have focused on cognitive factors as central components of psychiatric disorders.[1] Psychiatric disorders are defined by abnormalities of thought, affect, and impulse control. Arguably, the greatest functional impact of these illnesses on the lives of the mentally ill and society are not related to the symptoms of delusions, hallucinations, or depressed mood, but simply to making poor decisions. These decisions can contribute to behaviors such as nonadherence to medications or outpatient appointments, failing to exercise, poor diet, using drugs, or engaging in unprotected sex. Downstream consequences of poor decisions include worsening of symptoms, reduced life satisfaction, impaired everyday functioning, relapse and rehospitalization, clashes with law enforcement, poor physical health, and even more tragic outcomes such as accidental death, homicide, or suicide.

In many cases flawed decision making in mental illness is a product of the deficits in basic neuropsychological processes, including impaired attention, working memory, or response inhibition. Flawed decision making has a pervasive presence in clinical outcomes. For example, adherence rates for antidepressants, mood stabilizers, antipsychotics, or stimulants range between 30%−50%. More than half of the patients with severe mental illness are affected by substance use disorders. Forty percent of schizophrenic patients,

regardless of medication regimen, suffer from metabolic syndrome. Thus, addressing impaired decision-making processes should provide a valuable strategy to improve everyday functioning through an alteration of health status and treatment outcomes in psychiatric patients. In this monograph, the concepts used to characterize decision making are reviewed followed by a review of the known neural substrates that mediate the various elements of decision making. Last, the application of a decision-making approach to understanding some of the morbidity associated with mental illness is described.

DEFINING DECISION MAKING

A decision problem is defined by the actions or options among which one must choose, the possible outcomes or consequences of these actions, and the contingencies or conditional probabilities that relate outcomes to actions. Herbert Simon, a Nobel laureate, decomposed the task of rational decision making in three steps: (1) identification and delineation of all alternatives, (2) determination of the consequences of each alternative, and (3) a comparison of the accuracy and efficiency of each of these sets of consequences. Decision making is a constant process in modern life, that takes place from when we wake up until we *decide* to go to bed. Different disciplines, including psychology, psychiatry, neuroscience, economics, and neuroeconomics attempt to systematize the understanding of decision making.

Decision-making research paradigms range from electrophysiological to behavioral experiments (from insects to humans), lesion studies, and brain imaging. The paradigms used include monetary or nonmonetary positive- and negative-reinforcing stimuli (e.g., food, juice squirts, electric shocks) in order to assess an individual's reactions and choices. These paradigms allow for the exploration and characterization of interactions between individuals using economic principles (Table 1).

One of the many psychological theories focused on understanding behavior, drive theory, posits that organisms have needs, the primary needs related to survival, such as food and shelter, and secondary needs related to the organism's well-being and comfort. The goal of satisfaction of these needs drives organisms to action and represents the underlying motivation for behavior. When a need is satisfied, the drive is reduced and the person returns to a state of homeostasis and relaxation. An opposing view is promulgated in Skinnerian models,

which deny the existence of inner nonobservable phenomena, including motivation. Skinner defined operant conditioning and decision making as processes in which behavior is solely determined by its consequences, wherein organisms learn through experience to behave in ways in order to obtain rewards and avoid punishment. Thus, decision making is intrinsically related to previous experiences and their consequences.

Cognitive Control

Cognitive control refers to the ability to flexibly direct behavior in accordance with a variety of goals, and constitutes the ability to represent, maintain, and update the rules that guide behavior in a context-appropriate manner. Cognitive control functions include error detection and correction mechanisms, conflict resolution, response inhibition, task-switching, and emotion regulation. Although cognitive control functions were initially deemed to be a frontal cortex function, research in the last two decades has identified a "cognitive control network" that includes the dorsolateral prefrontal cortex (DLPFC), MPFC, ACC, parietal cortex, motor areas, and cerebellum.[2–5] Recent meta analyses of a very large Q:2 number of published functional magnetic resonance imaging (fMRI) datasets demonstrated that a superordinate frontal-cingulate-parietal-subcortical cognitive control system is engaged during the performance of a range of executive function tasks.[6] Functional connectivity has revealed that coordinated temporal activation across the network of prefrontal and posterior brain regions is associated with better performance on cognitive control tasks.[7] Impairments in the cognitive control system are seen in a variety of psychiatric disorders. For instance, deficits in emotion regulation are central to borderline personality and mood disorders, attention biases to negative stimuli are hallmark of anxiety disorders. Moreover, global impairments in cognitive control associated with deficits in attention, memory, language comprehension, and emotional processing are characteristic of schizophrenia, and responsible for this disorder's most disheartening clinical challenges (e.g., disorganization, negative symptoms) and functional outcome.

Reward and Value

A considerable amount of neuroscience research has been performed using the learning paradigm classical conditioning. Classical conditioning, prototypically illustrated by Pavlov's experiments, refers to the development of an automatic association between two co-

TABLE 1. Paradigms Used to Study Decision Making

Paradigm	Description	Neuropsychological target
Gamble/ lottery	Choice between possibilities associated with different outcomes	Calculation of expected utility and risk Risk can be dissociated from impulsivity
Iowa gambling task	Selection of cards of four different stacks with different monetary gains and penalties	
Cambridge gambling task	Probabilistic choice of finding a hidden token behind 10 boxes	Risk assessment without learning confounds
Wheel of fortune	Two choice task with probabilistic monetary outcomes	Targets separately reward and punishment processing
Ultimatum game	Two player game about how to split a pile of money. One makes an offer, and the other accepts or rejects it	Dissociation of profit from fairness expectations
Trust game	Two player game about sharing one's profits hoping for retribution from the other	Cooperation, trust, fairness, altruistic behavior
Prisoner's dilemma	Two player game about cooperating or defecting in a coordinated strategy	Cooperation, reciprocity, defection
Stag hunt	Two player game about	Risk assessment, mentalization

occurring, previously independent stimuli. The classic example is a dog's association of hearing a bell and the presentation of food thereby inducing salivation to subsequent sounding of the bell in the absence of the food stimulus. Seminal studies by Schultz et al. [8] examined brain responses during classical conditioning and showed increased phasic responses in the ventral tegmental area (VTA) dopaminergic neurons in primates when presented with an unexpected pleasurable stimulus or reward. These brain responses were subsequently evoked by a conditioned stimulus after pairings with the reward. Further, the activation of dopamine neurons decreased with extinction trials when the expected reward was omitted. Subsequent observations showed that these neurons actually fire in anticipation of future rewards. Thus, dopaminergic neurons seem to encode the likelihood of a rewarding outcome and generate a continuous update of its prediction accuracy. Dopamine is therefore believed to provide a teaching signal to parts of the brain responsible for acquiring new behaviors. Notably, serotonin closely interacts with dopamine along two different axes: reward (dopamine)-punishment (serotonin) and behavioral activation (dopamine) inhibition (serotonin).[9] The role of serotonin seems to counteract impulsivity, possibly by enhancing aversion and increasing behavioral inhibition. Although dopamine promotes behavioral activation to seek rewards, serotonin serves to inhibit actions when punishment may occur.

Neuroimaging experiments have identified dopaminergic projection areas, the orbitofrontal cortex (OFC) and ventral striatum [including the nucleus accumbens (NAcc)], as sites active during the learning, retention, and extinction conditions during reward processing.[10]

These two structures constitute the brain reward valuation system, which has been posited to mediate representation of a common neural currency.[11] Ventral striatal activation correlates with reward magnitude, whereas mPFC activation correlates with the probability of receiving a reward, reward anticipation, and saliency. However, the calculation of the different facets of reward and value are distributed along several brain regions, including the posterior cingulate cortex (PCC), ACC, the temporoparietal junction, including the inferior parietal lobule, superior temporal gyrus and anterior insula, and the left posterior parietal cortex.[12]

Risk, Uncertainty, and Ambiguity

Expected value, initially defined by Pascal, is the product of the payoff and estimated probability of occurrence of a possible choice, and represents a common internal currency that individuals use to compare and choose between different options to utilize resources (i.e., buying drugs versus groceries and medications).

The value of an item to an individual depends on the risk context. Thus, in an environment where the consequences of choices are certain and constant (Figure 1A, Figure 1B), the option with the highest value would be the preferred one.[13] However, since this situation is rarely encountered, expected value alone is often a poor predictor of choice. *Risk* is present when multiple possible outcomes can occur with well-defined or estimable probabilities (Figure 1C, Table 2). In **Q:3** economic models, risk is considered a cost and has to be weighed against the expected value of a decision. Sensitivity to risk is evidenced as risk aversion or risk-seeking behaviors. The incorporation of risk with reward or payoff led Bernoulli to posit the idea of subjective

FIGURE 1.   Decision Making Classified According to the Risk and Context Available Information

A) Stable environment; B) changing environment; C) stochastic environment; D) unknown environment; and E) interactive environment (Adapted From[13])

TABLE 2.   Decision Making Concepts and Their Neural Substrates

Concept	Definition	Neural substrate
Expected value and expected utility	Calculation of the combination of payoff and probability of occurrence a possible choice	Ventral striatum, medial prefrontal cortex, and orbitofrontal cortex
	Magnitude	Ventral striatum
	Probability	Medial prefrontal cortex
Uncertainty	Lack of knowledge of a decisions' outcome	Dorsomedial prefrontal cortex and anterior insula
Risk	Known unpredictable probability of an undesired outcome	Dorsomedial prefrontal cortex, amygdala, and anterior insula
Ambiguity	Unknown unpredictable probability of an undesired outcome.	Amygdala and insula
Temporal discounting	Decrease in the subjective value of a reward as a function of the amount of and delay to receive the reward	Interaction between impulsive (ventral striatum) and executive (dorsolateral prefrontal cortex, posterior parietal cortex) drives.
Regret	Reaction when a choice that resulted in a worse outcome than would have occurred with an alternative choice	Orbitofrontal cortex, superior frontal cortex, angular gyrus, and thalamus
Rejoice	Reaction when the option chosen yields a more favorable outcome than an alternative decision	Rostral anterior cingulate, hippocampus, ventral striatum, and midbrain
Dread	Reaction to waiting for a known future bad outcome	Caudal anterior cingulate and posterior insula

value or utility. Utility is the subjective assessment of the value of a reward; it is dynamic and can be influenced by the physiologic state of the individual (hunger, thirst, or sleep) and the context (home, inpatient unit, or prison). For instance, the challenge of keeping sobriety and taking prescribed medications is quite different for patients receiving ambulatory or inpatient care.

A more accurate analysis of real life situations requires the consideration of the interaction of uncertainty × context. *Uncertainty* refers to the lack of knowledge about the outcome of a decision and it can be associated with risk or ambiguity (Table 2). *Ambiguity* occurs in the presence of multiple outcomes whose probabilities are unknown or not well-defined, hence, the expected value

cannot be calculated (Figure 1D). Ambiguity is a more common real world situation and is even more aversion-provoking than risk. In the latter part of the last century, Kahneman and Tversky[14] developed *prospect theory*, which explains how humans calculate value nonlinearly. This view, supported by findings of nonlinear striatum activity, explains phenomena such as larger aversive response to losses compared with favorable response to comparable gains, strong preference for certainty, and cognitive biases as the framing effect (i.e., inconsistent choices dependent on whether a question is presented in terms of gains or losses).[14]

Risky choice tasks, such as facing a large reward associated with an unlikely outcome, versus a small

reward associated with a more probable outcome, lead to OFC activation.[15] Additionally, increased insular activation occurs when choosing riskier outcomes over safer outcomes[10,16] and amygdalar activation appears in anticipation of loss or punishment.[17] Gambling tasks revealed expected risk to be proportional to activation in the insula, lateral OFC, and midbrain,[18] and choices that maximized gains or minimized losses were predicted by activation in the ventromedial PFC (VMPFC) or anterior insula, respectively[19] Of these regions, the insula and the dorsomedial PFC (DMPFC)[20] have been shown to be predictive of uncertainty related to monetary[21] and nonmonetary stimuli.[22,23] In summary, the data support the view that the cognitive processing of uncertainty is related to the DMPFC, whereas the affective reaction is associated with the OFC and insula. Much of the data presented in this paper originates from fMRI. These data are usually obtained from the comparison of brain activation of a condition of interest and an adequate control, which is reflected in statistical maps that can be visualized as activation of particular brain regions or circuits. However, sensory perception, motor function, and cognition are the product of a coordinated action of several neural processes that occur below the temporal or spatial resolution of fMRI. Thus, it is important to avoid the temptation of assigning discrete mental operations to specific brain regions or circuits. Last, a practical example of abnormalities in uncertainty processing is the anticipatory anxiety found in panic disorder. Panic attacks can be such terrifying and helplessness-inducing experiences that patients live in fear of the next attack, uncertain when it will occur, thereby leading to progressively restricted lifestyles as futile attempts to prevent them.

Strategic Uncertainty

An even more realistic scenario when considering decision making in a social context is interaction with other individuals. Figure 1E shows the interaction between two individuals. In this type of interaction a decision maker needs to consider not only the inherent risk but also what the other person is likely to do, and how his/her own actions will affect others (strategic uncertainty). Strategic uncertainty can be studied with economic games that target the interaction between two or more people such as the prisoners' dilemma, the stag hunt, or the ultimatum game (Table 1). Paranoia is a prime example of a mental state that strongly influences the view of others and their attributed

intentions, and consequently the patient's own decision making that frequently leads to violence or isolation.

Game Theory

Game theory attempts to predict the strategies that a group of decision makers will converge on as they try to maximize their own profits. It rests on two basic assumptions: first, individuals only seek to maximize their own profit; and second, to achieve this they behave rationally. Nash equilibrium refers to a set of strategies from which no individual player can increase his payoff unilaterally. However, results from experiments in both human and nonhuman primates have systematically violated predictions from the Nash equilibrium. In humans, decision making in social contexts is not purely driven by self-interest, but also by considerations about the well-being of other individuals. Therefore, to better characterize decision making in social contexts, socially oriented emotions such as spite, fairness, and altruism need to be considered. The relevance of decision making within social contexts cannot be overestimated. For example, guilt is frequently found in abusive relationships in depressed patients; grandiosity and recklessness explain many of the interpersonal conflicts during mania; and paranoia and auditory hallucinations found in psychosis can strain interpersonal interactions to the point of violence.

Temporal Discounting

An additional dimension in decision making is time. We do not assign the same subjective value to rewards obtained in the present or in the future. *Temporal or delay discounting* is an operational measure of delayed gratification and has been shown to be altered in a number of conditions marked by impulsivity. This refers to the decrease in the subjective value of a commodity as the product of its amount and the delay to receive it.[24] For instance, if someone would prefer $80 now instead of $100 in 1 year, it could be said that the temporally distant $100 are discounted to an immediate value of $80. In a classical experiment, Mischel and collaborators presented preschool children the choice of one treat (cookie or candy) immediately, or having to wait several minutes for two treats. This task was Q:4 remarkably predictive of the childrens future life achievements. Children who preferred delayed larger rewards tended to be more intelligent, better able to concentrate, and more tolerant to frustration; and as adolescents had higher social-emotional and cognitive

function ratings, including academic performance.[25] Later follow up showed that the ability to wait as a preschooler predicted higher education achievements, and less risk for crack cocaine use.[26] This capacity to delay gratification has been associated with effective self-regulation through the use of abstract rather than consummatory strategies, as well as shifting of attention. Furthermore, in adolescents, a greater ability to delay gratification was associated with such characteristics as being responsible, productive, ethically consistent, interested in intellectual matters, overly controlled, and higher IQ, whereas those adolescents who were not able to delay gratification were characterized as rebellious, unpredictable, self-indulgent, or hostile.[27]

Temporal discounting is the outcome of opposing trends. The first, an instinctive response of craving immediate fulfillment of desires or needs, is linked to activation of medial OFC and subcortical structures, mainly the ventral striatum (VS).[28] The second, executive function, paradigm of cold cognition, reasoning, and planning, is associated with the activity of the right DLPFC and posterior parietal cortex.[29] The role of the PFC is further illustrated by the overwhelming preference for immediate rewards in patients with prefrontal damage in the so-called "environmental-dependency syndrome."[30] Activity in the mPFC, ventral striatum, and PCC are directly proportional to a reward magnitude, but inversely to the delay in time in which it is **Q:5** expected.[31] An attempt to separate the risk component in temporal discounting showed frontal pole, PCC, and the parahippocampal gyri to be associated with purely temporal computation.[32] Furthermore, when risky choices are dissociated from temporal ones, the former are associated with activation in DLPFC and posterior parietal cortex, whereas the later indicated activation of the PCC and the striatum.[33] These results suggest that cognitive processing of temporal discounting needs to integrate an element of risk and visualization of the future.

EMOTIONS AND DECISION MAKING

A traditional dichotomous view of hot emotion versus cold cognition has been refuted by research in neuroscience, psychology, and economics over the last decades. Emotion does not equate with irrationality, but is an altogether component of the decision-making process. Not surprisingly, the wide range of various emotions explains why is unrealistic to project all emotions into a one-dimensional category of pleasure versus pain.[34] Loewenstein and Lerner construe emotions according to their place along the time course of the decision process, including deliberation about a choice and the posterior reaction to the outcome.[35] They distinguish between *anticipated* and *immediate* emotions, with *immediate* emotions further classified into *incidental* and *integrated* emotions. *Anticipated* emotions are those believed to occur following a given decision outcome. This is also known as effective forecasting and typical examples are regret or disappointment. On the other hand, *immediate* emotions are those experienced while the individual is pondering a choice. Immediate emotions are either *incidental* emotions caused by factors, which are not related to the decision problem at hand, or *integral* emotions, which are caused by the decision problem itself.

On the other hand, Pfister and Bohm classify emotion according to its function emphasizing emotion's role in decision-making processes. They consider four categories: *information, speed, relevance*, and *commitment*.[36] The *information function* provides evaluative information which weighs in preference construction. Emotions such as joy or distress inform about the degree of (un) pleasantness of choices and consequences. They allow one to map a diversity of experiences on a one-dimensional scale of pleasure and pain. The *speed function* enables rapid choice and action under time pressure. Affect programs for negative emotions such as fear and disgust trigger immediate avoidance responses.[37] These mechanisms are highly stimulus-specific and presumably have evolved under evolutionary selection pressure. The somatic-marker hypothesis[38] maintains that these kinds of affective signals, originating in bodily states and acquired by learning from previous experiences, act as markers about the valence of current experiences. Somatic markers operate automatically and obligatorily, influencing behavior even before a conscious intention is generated. The *relevance function* focuses attention on particular aspects of potential relevance for the decision-maker. Emotions such as regret or envy constitute a particular appraisal, which implies particular evaluations as well as particular action tendencies. The *commitment function* enables social coordination by committing people to stick to decisions, even against their short-term self-interest. Guilt, altruism, love, or hate guide decision making in strategic choice situations. Overall, emotions do not have

TABLE 3. Insight Brought to Mental Illness Through Decision-Making Research

Condition	Decision-making abnormalities	Neural substrate
Depression and anhedonia	Deficits in reward processing	Hypoactive ventral and dorsal striatum Hyperactive orbitofrontal cortex
Drug addiction	Deficits in temporal discounting Exaggerated risk taking behavior	Hyperactivity of mesolimbic system (orbitofrontal and ventral striatum) and/or hypoactive executive system (dorsolateral prefrontal cortex and posterior parietal cortex)
Schizophrenia	Context processing Deficits in reward processing Deficits in temporal discounting	Hypoactive dorsolateral prefrontal cortex
Gambling	Illusion of personal control Near miss effect Loss chasing	Abnormal activity in ventromedial prefrontal cortex, ventral striatum anterior insula
Anorexia nervosa	Abnormal reward processing (quantitatively and qualitatively)	Abnormal activity in hypoactive ventral striatum

a uniform influence on decision making, but seem to be rather dependent on the context and in the individual circumstances. An example of the pervasive effect of emotion in mental illness is given by the abnormalities in reward processing found in anhedonia and depression (Table 3).[39]

UNCONSCIOUS DECISION MAKING

Unconscious knowledge refers to that revealed by task performance alone, subjects being unaware that they are accessing it, whereas we speak of conscious knowledge when subjects are aware of possessing and accessing it.[40] It ranges from basic perceptual processing to spontaneous problem solving. Even though attention to the unconscious had already been studied before Freud, his work had considerable impact on the 20th century's research on unconscious knowledge.[41] Unconscious or subliminal processing has been described in visual, auditory, somatosensory, and olfactory information. Experimental methods used to tap unconscious processes, include studying subjects who are unaware of the stimuli, because they are too weak, brief, complex, or are masked (i.e., subliminal perception). Other approaches examine states of complete unconsciousness (i.e., sleep, coma, and anesthesia), inability to be conscious of certain kinds of stimuli (i.e., blindsight, hemineglect, and prosopagnosia), or when attention has been diverted to another demanding task.

Examples of cognitive processes found to run at the unconscious level include task-set preparation, conflict detection/resolution, motivation, and error detection. (For detailed reviews see[42,43].) Several "high-level" (prefrontal) cognitive functions, such as response

inhibition and task-switching, space integration of multiple unconscious stimuli,[44] ensemble statistics,[45] and play recognition in expert chess players[46] have been observed to be influenced and modulated by subliminal stimuli. Priming research has shown that subliminal information can affect behavior and brain activity for a considerable amount of time, even 24 hours.[47] Last, although controversial, unconscious thought theory, with limitations and detractors, attempts to account for the existence of what it calls "the unconscious" in the empiric observations of people seeming to make better decisions when they leave it to "the unconscious" to do the job.[48]

DECISION MAKING IN MENTAL ILLNESS

Psychiatric disorders encompass a wide variety of nosological presentations traditionally classified as disorders of thought, affect, or impulse control. The pathophysiology of the vast majority of psychiatric disorders is complex and not well understood. There is a trend in psychiatry to explain mental illness with common denominators across diagnostic boundaries. One common element in severe mental illness is pervasive bad decision making (i.e., not taking medications, paying heed to command hallucinations, or attempting suicide). Despite the ubiquity of decision making in daily life, it has been largely neglected in the diagnosis and management of mental illness. Individuals' choices are intimately related to disease outcome (hospitalization, incarceration, or suicide), which have been largely unchanged despite decades of research in neuroscience, psychology, and psychiatry.

Depression

Major depressive disorder (MDD) is characterized by two primary affective symptoms: sustained negative affect and reduced positive affect.[49] In general, decisions during depressed states are tainted by negative affect and distorted negative cognitions,[50] although some research suggests that mild levels of depression may be associated with more realistic self-assessments even in psychotic patients.[51] A number of studies have used monetary and nonmonetary paradigms to evaluate the reward system in depression. A consistent pattern of reduced activation of the ventral striatum, dorsal striatum, and VMPFC[52–54] in response to positive reward stimuli has been reported, but see also for discrepant results.[55] A real life consequence of altered reward processing in depression was demonstrated in a report of economic social interaction using the ultimatum game in which participants were asked to accept or reject a wide range of offers. Depressed patients exhibited a more negative emotional reaction to unfair offers, despite accepting more of these offers than controls.[56] Thus, depression appears to have a dual effect on the processing of reward and value: induction of excessive emotional responses and reduced willingness to reject unfair offers.

There is considerable evidence that monoamine systems, including dopamine (DA) and serotonin, are altered in depression.[57] Considerable monoamine loss is observed in high-risk states for depression.[58] In particular, DA neurotransmission in major depressive disorder (MDD) seems to be diminished, either by decreased DA release or intracellular signaling processing. These DA-related disturbances improve by treatment with antidepressants, presumably by acting on serotonergic or noradrenergic circuits, which then affect DA function.[57] Furthermore, DA receptor binding and amphetamine response in depression are correlated with altered brain activation in the ventrolateral PFC, OFC, caudate, and putamen.[59] Overall, depression seems to be associated with an alteration of the prefrontal control over the striatum leading to a dysfunctional frontostriatal connectivity. The impact of the frontostriatal system dysfunction in depression can be further understood considering the role of two circuits: the medial prefrontal cortex-ventral striatum, which underlies motivation, and the OFC-ventromedial caudate, considered to intervene in affective processing.[60,61]

In addition of serotonin's role in impulsive aggression,[62–64] abnormal serotonin function has been linked to psychopathologies associated with negative affects such as depression and anxiety.[65–68] In contrast to impulsivity, depression is characterized by reduced behavioral vigor and enhanced aversive processing, with increased sensitivity to negative stimuli.[69] However, both impulsivity and depression have been associated with low serotonergic tone, based primarily on the therapeutic efficacy of selective serotonin reuptake inhibitors (SSRIs) and observations that central serotonin depletion through dietary manipulation can induce depressive relapse.[70,71] Indeed, patients with depression show reduced tryptophan levels,[72] abnormal serotonin receptor function,[73] abnormal serotonin transporter function,[74] and elevated brain serotonin turnover.[75] However, the relationship between depression and serotonin is less clear-cut than that between impulsivity and serotonin. It is possible that the link between depression and serotonin might be indirect and mediated by associative learning[76] and/or disinhibition of negative thoughts.[77] Overall, a number of psychiatric disorders seem to disrupt the delicate balance between serotonin and dopamine, reflecting alterations in reward, risk assessment, and social interaction. This view is supported by the wide pharmacological profiles of the major psychotropics, such as antidepressants, antipsychotics, and even drugs of abuse.

Anhedonia, which is the loss of pleasure or interest in previously rewarding stimuli, is a key pathological element of MDD and predicts antidepressant response.[78] Anhedonia is associated with disruption of the frontostriatal valuation system and reward processing (Figure 2). Anhedonic depressed patients exhibit reduced caudate[52] and OFC volume.[79] Decreased activation of the ventral striatum during reward selection, anticipation, and feedback are found in monetary tasks in nonmedicated anhedonic depressed patients.[80] Exploration of anhedonia in healthy volunteers showed decreased striatal activation and overactivation of the VMPFC during reward processing.[81]

There is debate as to whether anhedonia in depressed patients represents the inability to experience pleasure and engage in rewarding activities, or the inability to sustain positive affect. Neuroimaging data support both hypotheses. Epstein et al.[80] reported that unmedicated depressed patients exhibited decreased ventral striatum and DMPFC activation with positive stimuli. Additionally, the magnitude of ventral striatum deactivation correlated with decreased interest and pleasure during daily activities. In contrast, Heller et al.,[39] using an

FIGURE 2. Neuroanatomy of Decision Making
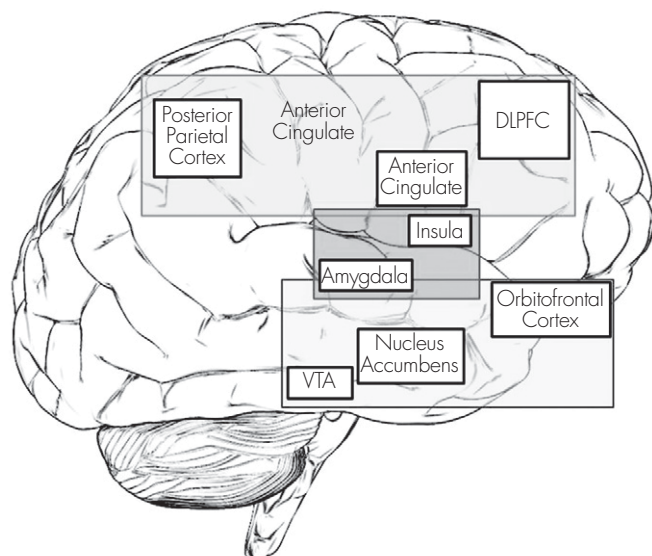
Areas in blue show the brain reward valuation system: ventral tegmental area (VTA) projections, ventral striatum (VS), and orbitofrontal cortex (OFC). (Areas in green show the substrates of executive function: dorsolateral prefrontal cortex (DLPFC) and posterior parietal cortex. Areas in red show two brain regions involved in emotion and intuition processing: amygdala and insula.

emotion regulation task found that depressed individuals were able to up-regulate positive affect, but failed to sustain NAcc activity over time. This diminished capacity to maintain positive affect was associated with decreased connectivity between the NAcc and mPFC. This concatenation of results points to an altered valuation system (frontostriatal circuit) in anhedonia, likely at the PFC level. This would be consistent with the therapeutic effects of psychotherapy such as cognitive behavioral therapy (CBT), which aims to identify and change dysfunctional patterns of thought and behavior. Furthermore, different forms of psychotherapy (e.g., interpersonal, behavioral activation, and cognitive behavioral therapy), for depression have shown normalization of PFC and striatum activity during reward tasks.[81,82]

Development Depressed adolescents exhibit similar alterations of the reward system as their adult counterparts. Children between 9 and 17 years old with MDD had reduced neural response than controls in the caudate, OFC, ACC, and amygdala, as well as higher neuroactivation in the DLPFC and frontal pole during

decision and outcome phases in a monetary reward task.[83] In addition, diminished caudate activation was correlated with lower subjective positive affect during follow-up.[83] The same group also reported that pretreatment striatal and medial PFC reactivity during a monetary reward task were predictive of response to cognitive-behavioral therapy (CBT) or pharmacological treatment. Relative to control subjects, adult individuals exposed to childhood adversity reported elevated symptoms of anhedonia and depression, rated the reward cues less positively, and displayed a weaker response to reward cues in the left globus pallidus.[84] Additionally, the combination of adverse early life experience and the short polymorphism of the serotonin transporter gene enhances negativity bias (perceiving more danger and risk than reward) and physiological reactivity to negative experiences.[49]

On the other hand, depression in older adults presents with unique cognitive characteristics. Individuals are guided by the same essential set of socioemotional goals throughout life, such as seeking novelty, feeling needed, and expanding one's horizons. However, the relative priority of different sets of goals changes as a function of age. Typically, despite being at risk for loss of loved ones, function, finances, and status, older adults endorse better well-being than younger counterparts. This apparent paradox is explained by the Socioemotional Selectivity theory[85], which states that according to the perception of time left to live, an individual's perceived limitations on time lead to reorganizations of goals thereby prioritizing those with emotional meaning over those that maximize long-term payoffs in the distant future. This is believed to occur through more effective cognitive control over negative affect which reflects in effective emotion regulation mediated by the ventral PFC.[86] However, in the less frequent cases when depression occurs in older adults, it is typically associated with vascular insults that affect the PFC function. Because late onset depression is usually secondary to the loss of coping cognitive mechanisms in the elderly, it tends to be treatment resistant and have poorer outcomes.

Suicide is the most catastrophic outcome of depression and other psychiatric disorders, and is associated with reduced serotonergic neurotransmission, particularly within the VMPFC, including increased expression of serotonin 1 and 2 receptors[87] and binding of the presynaptic serotonin $_2$ receptor in the VMPFC[88] (for review, see[89]). This dearth of serotonin is thought to

impair executive function, predisposing patients to become more impulsive, rigid in their thinking, and poorer decision-makers. Deficits in executive function and problem-solving are greater in depressed individuals with a history of suicide attempts or even suicidal ideation compared with depressed controls.[90] Impaired decision making, reflected in poor performance in the Iowa Gambling Task (IGT), which is designed to mimic complex and uncertain decision making, is found in individuals with a past history of suicide attempts,[91] in particular, in those that used violent methods.[92] Euthymic patients with a history of suicide attempts showed significant deficits in executive function: impaired visuospatial conceptualization, inhibition, and visual attention (or reading fluency) suggestive of generalized PFC dysfunction, both DLPFC and VMPFC.[93] It is possible that executive function deficits may be more specific to suicidal behavior rather than to any specific psychiatric diagnosis because this observation holds true for suicidal patients with depression, bipolar disorder, and even temporal lobe epilepsy. Last, poor inhibition is found in suicide attempters when compared with patients with only suicidal ideation,[94] and greater cognitive executive function impairments are found in depressed patients with suicidal ideation compared with those without it.[95] However, individuals with a history of suicide attempts show poorer inhibition but better problem-solving ability than suicide ideators.[94] There is evidence that at least a subgroup of suicide attempters have deficits in self-regulation and temporal discounting. Depressed suicide attempters 60 years or older showed deficits in probabilistic reversal learning suggesting that this population makes present focused decisions, ignoring past experiences.[96] In a similar elderly sample, Dombrovski et al.[97] showed decreased temporal discounting in high-lethality suicide attempters compared with low lethality ones.

Anxiety

Anxiety is the natural response to risk and uncertainty, both of which are frequently found in everyday life (see Figure 1). The amygdala plays a central role in mediating an anxiogenic response to unpredictability.[98] Additionally, the insula is a key structure involved in the prediction of risk,[18] and the DLPFC is positively correlated with risk aversion.[99]

Fear and anxiety are closely related, and share common cognitive and physiological properties.[100] Fear response is evoked by specific stimuli and tends to be transient, decreasing once a threat has dissipated. Anxiety may be experienced in the absence of a direct threat and typically persists over a longer period of time. However, anxiety is commonly conceptualized as a state of sustained fear.[101] Fear conditioning has been a most successful research model to understand the biology of anxiety. Animal and human research on fear conditioning has highlighted the central role of the amygdala in fear acquisition, storage, and expression.[101–103] The amygdala's projections to different parts of the brain have been associated with specific functions. For instance, projections to the brainstem and hypothalamus mediate autonomic fear expression, projections to the ventral striatum mediate the use of actions to cope with fear,[102] hippocampal projections are involved in contextually dependent expression of fear,[104] and connectivity to the VMPFC is required for inhibition or control of conditioned fear and storage of extinction memory[5,104,105]

Two principal information-processing biases are characteristic of anxiety: (1) a bias to attend toward threat-related information, and (2) a bias toward negative interpretation of ambiguous stimuli.[106] Anxiety is associated with faster response times when detecting a threat or negative stimuli or identifying a target cued by a threat stimulus, and slower response times when detecting a neutral stimulus or reporting neutral information in the presence of a threat stimulus.[107–109] This attentional bias reflects both facilitated detection of threat-related stimuli and difficulty in disengaging attention from negative stimuli,[107] and seems to be related to both the engagement of preattentive amygdala-dependent threat evaluation processes[110] and impaired prefrontal control mechanisms typically engaged during attentional competition and control.[111] Consistent with this view, high trait anxiety is associated with increased amygdala activity to attended as well as unattended threat stimuli[112] and decreased prefrontal activation under conditions of attention competition,[111,112] even in the absence of threat-related stimuli.[113]

Anxious individuals unrealistically judge negative outcomes to be more likely than positive ones.[114–116] Higher trait anxiety is associated with heightened amygdala blood-oxygen-level-dependent (BOLD)-responses during passive viewing of neutral faces[117] and a tendency to interpret neutral faces more negatively.[118] For instance, anxious individuals tend to interpret ambiguous emotional facial expressions,[119]

face-voice pairings,[120] and homophones[121] as more negative in valence than less-anxious individuals.

Anxiety as a trait has been amply studied in healthy subjects. Trait anxiety, worry, and social anxiety in healthy participants are predictive of heightened risk aversion.[122–124] In turn, heightened arousal to risky choices or increased interoceptive awareness of arousal responses (or an interaction of the two) may lead anxious individuals to be more risk averse. Trait anxiety is also associated with greater susceptibility to the framing effect (i.e., reacting differently whether a choice is presented in terms of gain or loss).[125]

The circuitry involved in the learning and regulation of conditioned fear is altered in healthy individuals with the anxiety trait and in patients suffering from anxiety disorders. Trait anxiety is associated with heightened amygdala activation as well as elevated fear expression during fear acquisition.[126,127] Anxiety also impairs extinction learning and retention[126–128] as well as the regulation of emotional responses via intentional cognitive strategies.[107,129] Patients with panic disorder show an increased generalization of conditioned fear to similar stimuli.[130] Atrophy of the hippocampus in posttraumatic stress disorder patients suggests that contextual modulation of fear may also be altered in anxiety.[131]

Although clinical data are still limited,[105] there is clear evidence of negative attentional biases in several anxiety disorders including generalized anxiety disorder, posttraumatic stress disorder, social and specific phobias, and obsessive-compulsive disorder (for review see[107]). Amygdala hyper-responsivity while attending to, evaluating, and anticipating negative stimuli may heighten the cognitive and affective responses to a potential threat in anxious individuals. Thus, the everyday decisions made by individuals suffering from anxiety disorders to avoid exaggerated perceived threats can have a profound impact on the ability to function adaptively.

Bipolar Disorder

Bipolar disorder and schizophrenia share impairments in similar cognitive areas including attention, processing speed, verbal memory, learning, and executive function, although bipolar disorder deficits are usually less severe.[132] These cognitive impairments represent a substantial clinical problem in up to 60% of bipolar disorder patients[133] and can be found in depressed, manic, and mixed episodes as well as in the euthymic state. This pervasive impairment in cognitive function in bipolar disorder suggests it may be a trait marker associated with genetic vulnerability.

A real life consequence of these cognitive deficits is functional impairment in several spheres including independent living, social relationships, and vocational success. For instance, 20% of patients with bipolar disorder are married in contrast to 60% of the general population; approximately 60% of bipolar patients are unemployed compared with 6% in the general population; and 19%−58% are not living independently.[134] These functional impairments are present at the time of the first episode and persist over time.[135]

In addition to the pervasive alterations in the cognitive sphere, emotion processing is markedly disrupted in patients suffering from bipolar disorder. It has been proposed that central to bipolar disease is a heightened processing of positive emotion regardless of the context.[136] A recent meta-analysis identified significant deficits in theory of mind and emotion processing in euthymic bipolar patients.[137] Emotion processing in depressed bipolar patients appears to involve a partially overlapping neural network with that of major depression, but with distinct roles of the VLPFC and thalamus.[138] Thus, bipolar patients are impaired in their ability to identify other individuals' emotions and intentions, with a resultant impact on everyday functioning.

Despite these deficits in cognition and emotion processing, the findings on decision making are heterogeneous in bipolar disorder. For instance, manic or hypomanic patients tend to make suboptimal choices in the Cambridge Gambling Task,[139] they are more sensitive to error processing during a two choice prediction task,[140] they show steep temporal discounting,[141] and deficits in response disinhibition and inattention ([142], but see also[143,144]). These deficits are not exclusive to mania, since depressed bipolar patients evidence deficits in reward processing, short-term memory, and sensitivity to negative feedback.[145] Moreover, euthymic patients with bipolar disorder also display moderate to severe deficits in a wide variety of executive function measures including category fluency, mental manipulation, verbal learning, abstraction, set-shifting, sustained attention, response inhibition, and psychomotor speed ([146–148], but see also[91,149,150]). Furthermore, even first degree relatives of bipolar disorder patients show executive function deficits (i.e., attentional set shifting).[151] In addition to moderate to severe neuropsychological impairments, there seems to be

specific cognitive and decision making biases in bipolar patients including impulsivity, exaggerated positive emotion, and deficits in risk assessment and reward processing. The weights of these cognitive and decision-making impairments are evident in the somber functional outcomes of patients with bipolar disorder.

Schizophrenia

Schizophrenia is a severe psychiatric disorder that afflicts approximately 1% of the population worldwide. It is characterized by alterations in higher function including thought, perception, mood, and behavior. The majority of people with schizophrenia do not attain "normal" milestones in social functioning, productivity, residence, and self-care. For instance, less than 20% of schizophrenic patients are responsible for their housing, almost 80% are unemployed, and less than 15% are married or in stable relationships.[152] This functional impairment occurs despite adequate symptom control that is attained by 30%–70% of patients. A large body of evidence has demonstrated significant cognitive dysfunction in schizophrenia, which is associated with disorganization, negative symptoms, and impaired functional outcome.[153] Information-processing deficits in schizophrenia are described in attention, working memory, inhibition, and context processing.[154] Context-processing deficits are associated with working memory impairments and dopaminergic tone in the PFC (Table 3).[155] Moreover, both cognitive control and social cognition (e.g., theory of mind) deficits are disease outcome predictors and suitable candidates for therapeutic interventions.[152,156] It is no surprise that this faulty information processing in schizophrenic patients translates into impaired risk assessment,[75,76] reward processing,[157] and temporal discounting.[158,159] The latter are correlated with working memory deficits.[159,160]

A pervasive clinical challenge in schizophrenia is the elevated comorbidity with substance abuse disorders. Approximately half of schizophrenic patients present a lifetime history of substance abuse disorders,[161] and 75%–90% are current smokers.[162,163] These extraordinary high rates of substance-use comorbidity may be explained by disrupted reward processing.[164] Thus, patients with schizophrenia who are smokers display a stronger subjective response and intensity of demands to smoking than the general population smokers.[165,166] In sum, patients with schizophrenia exhibit global cognitive control dysfunction that is reflected in specific deficits in risk assessment, reward processing, and temporal discounting. These impairments are translated in the devastating functional toll of this disorder.

POSSIBLE INTERVENTIONS

There are already successful therapeutic approaches focused on improving cognition and decision-making capabilities of psychiatric patients: cognitive remediation and variations of cognitive-behavioral therapy (CBT), which aim to enhance emotional cognitive control and decision-making skills. Cognitive remediation is based on enhancing specific cognitive processes in order to modify the course and morbidities of disease. Recent advances in cognitive remediation strategies and delivery methods have notably increased the success of this intervention.[167] These advances include (1) the development of multidimensional tests of executive functioning that drill and practice with low-level cognitive demands, (2) the dynamic adjustment of difficulty in order to maintain a constant difficulty level, and (3) the development of understanding the minimum effective dose and optimal spacing of practice trials. Successful examples are found in areas as diverse as schizophrenia,[168] bipolar disorder,[169] attention deficit hyperactivity disorder (ADHD),[170] dyslexia,[171] traumatic brain injury,[172] and stroke.[173] In these studies, cognitive remediation was associated with improvement in hyperactivity, organizational skills, affect, sustained attention, and temporal discounting.[174] Moreover, improvements induced by cognitive remediation correlate with discrete changes in neural activity,[175] noneffortful auditory evoked potentials,[176] peripheral biomarkers as brain-derived neurotrophic factor (BDNF),[177] as well as improvements in everyday functioning. Furthermore, considering the close association between cognitive impairments and poor functional outcome, cognitive remediation aimed at social cognitive impairments has proven effective in enhancing social functioning. Social cognitive remediation programs are either targeted to a specific social cognitive domain (e.g., emotion perception), or broad-based, combining a variety of psychosocial approaches, including cognitive remediation, social skills training, and social cognitive skill building.[178,179] Both approaches have proved effective in improving social cognitive processes in schizophrenia.[180,181]

Two examples of the successful adaptation of cognitive-behavioral therapy to enhance decision making are dialectical behavior therapy and problem-solving therapy. Dialectical behavior therapy (DBT) was the first

psychological treatment for borderline personality disorder tested in a clinical trial.[182] It is specifically designed to target the emotion dysregulation (mood instability) and to reduce impulsive behaviors (in other words, enhancing emotional cognitive control). It applies behavioral analysis to incidents leading to self-injury and overdoses, teaching patients alternative ways to handle dysphoric emotions. DBT has been used successfully in patients with borderline personality disorder, eating disorders, and parasuicidal behavior. Problem-solving therapy (PST) is a cognitive-behavioral intervention that focuses on training in adaptive problem-solving attitudes and skills.[183] It aims to reduce and prevent psychopathology and enhance positive well-being by helping individuals cope more effectively with stressful problems in living. PST is based on a relational/problem-solving model of stress and well-being (psychological, social, and health functioning) in which *social problem solving* (i.e., real-life problem solving) is assumed to play an important role as a mediator and a moderator of the relationship between stressful life events (major negative events as well as daily problems) and well-being. It has proven effective for the treatment of depression.[184]

CONCLUSIONS

It is not surprising that severe mental illness affects patients' lives not only because of the cardinal disease symptoms, but also by impairing their ability to make functional and healthy decisions. This impairment may be related to disorganization or global deficits in attention, working memory, and language, such as those observed in schizophrenia and bipolar disorder. However, it can be subtler and lead to abnormal risk assessment or reward processing as found in depression. These pervasive deficits translate into medication and medical appointment nonadherence, poor diet and exercise, and drug use, which in turn leads to poor quality of life and clinical outcomes such as relapse, hospitalization, death, and incarceration.

A multidisciplinary approach to how the brain makes decisions may provide a new theory of thought with quantifiable parameters that can increase understanding of mental processes (decision making) in health and disease. The study of two particular constructs, reward and temporal discounting, has shed light on our understanding of severe mental illness. The utilization of additional paradigms can further lead to interventions to address every day situations that patients with mental illness face. The consideration of decision-making patterns in the assessment and management of patients with mental illness might yield evidence-based interventions with real life impact such as cognitive remediation.

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AUTHOR QUERIES

AUTHOR PLEASE ANSWER ALL QUERIES

1—Please supply a brief left running head.

2—In the sentence beginning "Although cognitive control...," please define MPFC and ACC.

3—In-text callouts for Tables 2 and 3 and Figure 2 were not included. Please confirm whether our locations for these callouts are okay.

4—In the sentence beginning "In a classical experiment...," please provide the reference number for "Mischel and collaborators."

5—In the sentence beginning, "Activity in the mPFC...," please note that in the section "Cognitive Control," "mPFC" is written as "MPFC." Should both be set the same?

6—Reference 91 was modified to reflect the literature (pub year was changed from 2010 to 2011; page range was changed from 1–9 to 1319–1327).