Trait-Related Decision-Making Impairment in the Three Phases of Bipolar Disorder

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Background: In bipolar disorder (BD), little is known about how deficits in neurocognitive functions such as decision-making are related to phase of illness. We predicted that manic, depressed, and euthymic bipolar patients (BPs) would display impaired decision-making, and we tested whether clinical characteristics could predict patients' decision-making performance.

Methods: Subjects ($N = 317$; age range: 18–65 years) including 167 BPs (45 manic and 32 depressed inpatients, and 90 euthymic outpatients) and 150 age-, IQ-, and gender-matched healthy control (HC) participants, were included within three university psychiatric hospitals using a cross-sectional design. The relationship between predictor variables and decision-making was assessed by one-step multivariate analysis. The main outcome measures were overall decision-making ability on the Iowa Gambling Task (IGT) and an index of sensitivity to punishment frequency.

Results: Manic, depressed, and euthymic BPs selected significantly more cards from the risky decks than HCs ($p < .001$, $p < .01$, and $p < .05$, respectively), with no significant differences between the three BD groups. However, like HCs, BPs preferred decks that yielded infrequent penalties over those yielding frequent penalties. In multivariate analysis, decision-making impairment was significantly ($p < .001$) predicted by low level of education, high depressive scores, family history of BD, use of benzodiazepines, and nonuse of serotonin and norepinephrine reuptake inhibitor (SNRI) antidepressants.

Conclusions: BPs have a trait-related impairment in decision-making that does not vary across illness phase. However, some subtle differences between the BD groups in the individual deck analyses may point to subtle state influences on reinforcement mechanisms, in addition to a more fundamental trait impairment in risk-sensitive decision making.

Key Words: Bipolar disorder, decision making, depression, euthymia, mania, neurocognition

It is now accepted that bipolar disorder (BD) is associated with substantial alterations in neuropsychologic function. Whereas early studies focused on attentional, mnemonic, and executive domains, recent studies have highlighted the link between simple tests of risky decision-making and the manic phase of the illness (1,2). Although trait-related cognitive impairments have been reported in BD patients (BPs) (3,4), the nature and extent of decision-making dysfunction across the phases of the illness remain unclear. Some studies have shown that patients have impaired decision-making in both the manic (1,2, 5–7) and depressed (8) states, whereas others have reported conflicting results in patients in remission (9–13). It is also likely that other illness variables, such as number of episodes, severity of acute symptoms, type of medication, and family history of BD have an impact on decision-making cognition. To our knowledge, Yechiam *et al.* (13) are the only group that has used the same task to assess decision-making in both the acute and remitted state of BD. However, their study was limited by small group sizes and lack of power.

Decision-making occurs when the individual has to select between multiple options associated with uncertain consequences. Laboratory tasks have been devised to assess competency in real-world decision-making and dissect some of cognitive processes involved. This study used the Iowa Gambling Task (IGT), a clinically sensitive tool that emulates real-world financial decision-making. Each choice leads to monetary gains or losses. Differences in IGT performance are seen in individuals with neuropsychiatric disorders characterized by problems in impulse control and emotional regulation (14–17). Functional imaging (17,18) and brain lesion studies have implicated distributed neural circuitry in supporting successful decision-making on the IGT, including the ventromedial (ventromedial prefrontal cortex [VMPFC]) (19) and ventrolateral prefrontal cortex (20), and amygdala (21), areas that have been associated with BD (22).

On the basis of these findings, we predict that decision-making is impaired in the acute phases but also in remission of BD. The IGT results were further analyzed in relation to sociodemographic and clinical variables in BD patients.

Methods and Materials

Participants

The study population comprised 167 BPs (98 women and 69 men; age range: 18–65 years) and 150 healthy volunteers (75 women and 75 men; age range: 19–64 years; see power analysis in Section 1 of Supplement 1). Diagnostic assessment of the patients

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was initially performed by an experienced psychiatrist and was confirmed using the Structural Clinical Interview for DSM-IV (23). Exclusion criteria included a history of head injury or neurologic disease. All subjects had normal thyroid function. No patient had received electroconvulsive therapy or had a history of substance abuse within the previous 6 months. Control subjects had no psychiatric history, no first-degree relatives with BD, and were not taking any drugs that might affect cognition. The study was approved by the local ethics committees. After complete description of the study to the subjects, written informed consent was obtained.

Manic Group

Forty-five inpatients suffering from mania were included (30 from Marseille University Department of Psychiatry and 15 from Oxford University Department of Psychiatry). All patients met the DSM-IV criteria for bipolar I disorder, manic episode, with a score greater than 12 on the Young Mania Rating Scale (YMRS) (24) and less than 7 on the Hamilton Depression Rating Scale (HDRS, 17 items) (25). The manic group comprised 22 women and 23 men (age range: 18–65 years). Thirty-two of the 45 patients were receiving antipsychotic drugs at the time of testing. No patients were receiving D_2-agonist antipsychotics. Fifteen patients were receiving typical antipsychotics. Seventeen patients were receiving the atypical antipsychotics risperidone ($n = 1$), clozapine ($n = 1$), and olanzapine ($n = 15$). Fourteen of these patients were also receiving lithium, valproate, carbamazepine, or a combination of these drugs. Eleven patients were receiving lithium, valproate, carbamazepine, or a combination of these drugs without a neuroleptic. Twenty-three patients were receiving a benzodiazepine, typically diazepam or lorazepam.

Depressed Group

Thirty-two inpatients suffering from bipolar depression were included (16 from Marseille University Department of Psychiatry and 16 from Montpellier University Department of Psychiatry). All patients met the DSM-IV criteria for bipolar I disorder, depressed episode, with a score of greater than 12 on the HDRS) (25) and less than 7 on the YMRS (24). The depressed group comprised 18 women and 14 men (age range: 22–63 years). Sixteen of the 32 patients were receiving antipsychotic drugs at the time of testing. No patients were receiving typical antipsychotics. Sixteen patients were receiving the atypical antipsychotics aripiprazole ($n = 3$), olanzapine ($n = 7$), risperidone ($n = 4$), amisulpride ($n = 1$), and clozapine ($n = 1$). Fourteen were also receiving lithium, valproate, carbamazepine, or a combination of these drugs. Thirteen patients were receiving lithium, valproate, carbamazepine, or a combination of these drugs without a neuroleptic. Sixteen patients were receiving lithium, valproate, carbamazepine, or a combination of these drugs with an antidepressant. Sixteen patients were receiving a benzodiazepine.

Euthymic Group

Ninety bipolar patients in clinical remission were included (60 from Montpellier University Department of Psychiatry and 30 from Oxford University Department of Psychiatry). All patients were euthymic at the time of testing, as defined by a score of less than 8 on the HDRS (25) and less than 8 on the YMRS (24), and met the DSM-IV criteria for bipolar I disorder, euthymic state. The euthymic group comprised 58 women and 32 men (age range: 18–65 years). Fifty-two of the 90 patients were receiving lithium, valproate, carbamazepine, or a combination of these drugs. Twenty-two patients were also receiving antipsychotics. Six patients were receiving typical antipsychotics. Seventeen patients were receiving the atypical antipsychotics aripiprazole ($n = 1$), risperidone ($n = 5$), and olanzapine ($n = 11$). Thirty patients were receiving lithium, valproate, carbamazepine, or a combination of these drugs without an antipsychotic. Thirty-eight patients were receiving lithium, valproate, carbamazepine, or a combination of these drugs with an antidepressant. Twenty-three patients were receiving a benzodiazepine.

Control Group

One hundred fifty healthy volunteers were recruited as control subjects by advertisements in the three communities (15 from Marseille, 30 from Oxford, and 105 from Montpellier). Control subjects had no psychiatric or neurological history, no first-degree relatives with BD, and were not taking any drugs that might affect cognition.

Procedure

Patients' mood was formally assessed using the YMRS and HDRS. Level of education and National Adult Reading Test (NART) (26) were used indirectly to assess premorbid intelligence level in the four groups (Table 1). NART *Z* scores were defined as the *Z* standardization scores of NART and fNART (French language adaptation of the NART) (27) scores, for English and French participants, respectively. Descriptive data for the 30 manic patients from Marseille, 15 manic and 30 euthymic patients from Oxford, and 60 euthymic patients from Montpellier have been published previously (1,5,12,14).

Iowa Gambling Task

The computerized version of the IGT (19) was used in which the participant plays for a pretend monetary reward. The participant is required to make a series of 100 choices from four decks of cards, labeled A, B, C, and D. Each card choice results in a monetary win, but occasional choices also result in monetary loss, and the four decks differ in the profile of wins and losses. At the start of the task, the participant has no information about the four decks and must learn to choose advantageously based on trial-by-trial feedback. Penalties begin after 15 picks of cards.

Decks A and B are associated with high immediate wins ($100/choice) but occasionally larger penalties that result in a net loss over time. Decks C and D are associated with smaller immediate wins ($50/choice) but lower long-term losses, such that participants accumulate gradual profit from choosing these decks.

Decks B and D provide low-frequency but high-magnitude penalties (with a ratio of total wins to total losses higher in deck D than in deck B, whereas decks A and C provide high-frequency but low-magnitude penalties (with a ratio of total wins to total losses higher in deck C than deck A). Thus, profitability of the decks (C + D vs. A + B) is orthogonalized from punishment frequency/magnitude (B + D vs. A + C).

Statistical Analysis

Choices in the IGT were analyzed for individual decks A, B, C, and D (Section 2 of Supplement 1), over five blocks of 20 trials (Figure 1) and over 100 picks of cards (Figure 2), and classified as advantageous ("safe") for decks C and D and disadvantageous ("risky") for decks A and B. The overall net score or decision-making ability is the difference between the total number of advantageous and disadvantageous choices. Net scores were calculated for each block of 20 trials (Figure 1), for the first 40 and the last 60 trials (Figure 3, Section 3 of Supplement 1). Data were also analyzed in terms of sensitivity to punishment frequency by calculating a difference score [(B + D) –