CHARACTERIZING DECISION-MAKING AND REWARD PROCESSING IN BIPOLAR DISORDER: A CLUSTER ANALYSIS.

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ABSTRACT

The presence of abnormalities in emotional decision-making and reward processing among bipolar patients (BP) has been well rehearsed. These disturbances are not limited to acute phases and are common even during remission. In recent years, the existence of discrete cognitive profiles in this psychiatric population has been replicated. However, emotional decision making and reward processing domains have barely been studied. Therefore, our aim was to explore the existence of different profiles on the aforementioned cognitive dimensions in BP.

The sample consisted of 126 euthymic BP. Main sociodemographic, clinical, functioning, and neurocognitive variables were gathered. A hierarchical-clustering technique was used to identify discrete neurocognitive profiles based on the performance in the Iowa Gambling Task. Afterward, the resulting clusters were compared using ANOVA or Chi-squared Test, as appropriate.

Evidence for the existence of three different profiles was provided. Cluster 1 was mainly characterized by poor decision ability. Cluster 2 presented the lowest sensitivity to punishment. Finally, cluster 3 presented the best decision-making ability and the highest levels of punishment sensitivity. Comparison between the three clusters indicated that cluster 2 was the most functionally impaired group. The poorest outcomes in attention, executive function domains, and social cognition were also observed within the same group.

In conclusion, similarly to that observed in “cold cognitive” domains, our results suggest the existence of three discrete cognitive profiles concerning emotional decision making and reward processing. Amongst all the indexes explored, low punishment sensitivity emerge as a potential correlate of poorer cognitive and functional outcomes in bipolar disorder.

INTRODUCTION

It has been widely proven that bipolar patients present cognitive impairment even in euthymic periods (Grande et al., 2016). Amongst all domains, attention, verbal memory, and executive function have been pointed out as the most affected areas in this group of patients (Bora et al., 2009;Miskowiak et al., 2017). Despite not being studied as exhaustively as the cognitive domains that make up the so-called "cold cognition", in recent years, there is a growing interest in the study of those domains where emotional processing is involved. Out of all studies, those on affective decision-making as well as reward processing were which led the way on the study on “hot cognitive domains”. These types of studies usually examine how bipolar patients weigh up different alternatives associated with variable degrees of reward and punishment using a variety of paradigms attempting to mimic real-life decision-making processes (Samame, 2013). To date, studies in the field have examined different aspects of reward processing in bipolar patients, including responses to various types of positive stimuli, affective response to rewards, and aspects of decision making or judgments, which target similar regions of the brain. Among all paradigms used, it should be remarked the relevance of the Iowa Gambling Test (IGT) (Bechara et al., 1994) which, indeed, has been recommended by the NIMH RDoC workshop on Positive Valence Systems as a measure of approach motivation (NIMH, 2011). Overall, several studies in this field have consistently reported poorer outcomes on both decision-making abilities as well as response to reward in bipolar patients compared to healthy controls (Adida et al., 2008;Brambilla et al., 2013;Malloy-Diniz et al., 2009;Powers et al., 2013;Roiser et al., 2009a;Strakowski et al., 2009). More specifically, different studies confirm that bipolar patients underperform in the IGT independently of mood state, even during euthymia (Adida et al., 2011;Edge et al., 2013), and have shown that increased risk

taking goes beyond manic states, being also elevated in patients presenting acute depression (Rubinsztein et al., 2006). Concerning sensitivity to punishment, some studies have reported that bipolar patients, in general terms, are more prone to avoid high-frequency penalties options (Adida, Jollant, Clark, Besnier, Guillaume, Kaladjian, Mazzola-Pomietto, Jeanningros, Goodwin, Azorin, and Courtet, 2011;Adida et al., 2015;Powers, Russo, Mahon, Brand, Braga, Malhotra, and Burdick, 2013) even during remission periods. Thus, bipolar disorder is characterized by both impaired reward processing and decision-making ability. Nonetheless, it remains unknown whether these deficits precede illness onset or are a consequence of the disease.

Besides, recent studies agreed that cognitive impairment observed among bipolar population seems to adjust to different profiles of severity. Different independent studies have identified three distinct cognitive profiles among bipolar patients: an intact group, which present a preserved neuropsychological performance; a selectively impaired group, whose neurocognitive performance is only significantly affected in few cognitive domains; and lastly, a global cognitively impaired group (Burdick et al., 2014;Jensen et al., 2016;Jimenez et al., 2017;Lewandowski et al., 2014;Sole et al., 2016;Van Rheenen et al., 2017). Nonetheless, these conclusions raised from studies mostly focused on “cold cognitive” domains, and none of these studies considered the performance on the IGT to carry out their analysis.

Therefore, our goal was to explore the existence of discrete cognitive profile in bipolar population according to their performance in the IGT. We hypothesized that, similar to what happens with the “cold cognitive” domains, heterogeneous profiles involving decision-making ability, risky choices, and punishment sensitivity would exist among bipolar patients, and that different clinical, neurocognitive and functional variables would be linked to each subgroup of patients.

EXPERIMENTAL PROCEDURES

Participants

One-hundred and twenty-six euthymic bipolar outpatients were recruited from the Bipolar Disorder Program of the Hospital Clinic of Barcelona and Mental Health Services from Oviedo, both under the umbrella of the Spanish Research Network on Mental Health (CIBERSAM).

Participants were selected only if they fulfilled the following inclusion criteria: (i) DSM-IV-TR criteria for bipolar I or bipolar II disorder (ii) age over 18 years, (iii) meeting criteria for euthymia for at least three months before inclusion assessed by means of the Hamilton Depression Rating Scale (HDRS)(Ramos-Brieva et al., 1986) and the Young Mania Rating Scale (YMRS) (Colom et al., 2002)(criteria was set out at HDRS≤8 and YMRS ≤6) and (iv) obtaining both written and verbal informed consent from all participants. Exclusion criteria were the presence of (i) intelligence quotient (IQ) lower than 70, (ii) the presence of any medical condition affecting neuropsychological performance, and (iii) electroconvulsive therapy within the past year. Concerning pharmacological treatment, no restrictions were made, including the use of benzodiazepines, in order to capture a representative sample of bipolar population. Nevertheless, all the patients were instructed to not take benzodiazepines 12 hours prior to the neuropsychological assessment. This study was approved by each institution's ethics committees and was carried out in accordance with the ethical principles of the Declaration of Helsinki.

Assessment

Sociodemographic, clinical and functioning variables

All participants were evaluated by means of a semi-structured interview based on the Structured Clinical Interview for DSM Disorders (SCID) in order to collect main sociodemographic and clinical data. Medical records were also reviewed and considered. The

severity of depressive and manic symptomatology was assessed by means of the HDRS and YMRS, respectively.

Level of functioning was gathered through the administration of the Functioning Assessment Short Test (FAST)(Rosa et al., 2007). This brief interviewer-administered scale, which comprises 24 items, assesses six specific functioning domains: autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationships and leisure time. Higher scores indicate a greater degree of functional impairment, being 72 the highest possible value (Rosa *et al.*2007).

The Barratt Impulsiveness Scale (BIS-11) (Patton et al., 1995) was used to evaluate trait-impulsivity. This self-rated 30-item questionnaire comprises three subscales: attentional-cognitive, motor, and non-planning impulsivity. Scores range from 30 to 120, with higher scores indicating greater impulsivity.

Suicidal ideation and behavior were rated by means of the Columbia Suicide Severity Rating Scale (C-SSRS) (Al-Halabi et al., 2016;Posner et al., 2011). This semi-structured interview assesses four constructs through four subscales: suicidal ideation, intensity of ideation, suicidal behavior and lethality. Suicidal profiles were established as set out in a previous work (Jimenez et al., 2016) as follows: patients who scored less than or equal to 1 at the *Suicidal Ideation* subscale were considered as non-suicidal patients. The remaining patients were in turn grouped into two groups ("history of suicidal ideation" and "history of suicidal ideation and behavior") according whether or not they fulfilled criteria for the Actual Attempt item from the *Suicidal Behavior* Scale.

Neurocognitive assessment

All participants were evaluated using a comprehensive neuropsychological battery based on a wide review of the existing literature in the field, in order to assess different cognitive domain performance.

- The estimated IQ was calculated based on the performance on the Vocabulary subtest from the Wechsler Adult Intelligence Scale (WAIS-III) (Wechsler D., 1997).
- The Processing speed domain comprised two subtests of the WAIS-III: the Symbol Search and the Digit-symbol Coding subtests (Wechsler D., 1997), the Trail Making Test-Part A (TMT-A) (Reitan.R.M., 1958), and the Categorical (Animal Naming) and the Phonemic (F-A-S) components of the Controlled Oral Word Association Test (COWAT) (Benton et al., 1976).
- Three subtest from the WAIS-III: Arithmetic, Digits, and Letter-Number sequencing composed the Working memory index (WM) (Wechsler D., 1997).
- The California Verbal Learning Test (CVLT) (Delis et al., 1987) was used to test Verbal Learning and Memory performance.
- Visual memory and learning was assessed through the Rey Osterrieth Complex Figure (ROCF) (Rey, 1997).
- The computerized version of the Continous Performance Test (CPT-II)(Conners, 2002) was used to explore Attention.
- The executive functions were measured by means of different tests examining response inhibition, set shifting and planning, specifically, the Stroop Color-Word Interference Test (Golden, 1978), the computerized Wisconsin Card Sorting Test (WSCT)(Heaton, 1981) and Trail Making Test-Part B (TMT-B) (Reitan.R.M., 1958).
- The Mayer–Salovey–Caruso Emotional Intelligence Test, version 2.0 (MSCEIT) (Brackett et al., 2006;Extremera et al., 2006) was used to evaluate Social Cognition, more specifically Emotional Intelligence.

Decision-making and reward processing were assessed by means of the computerized version of the IGT (Bechara et al., 1994). In this task, participants are asked to choose cards from four different decks (A, B, C, and D). Each card selected results always in a gain and, for some cards, also a loss. The goal of the task is to earn as much money as possible.

On the one hand, there are two "risky" decks (A and B) and two "safe" decks (C and D). Despite cards from the "risky" decks imply, on average, a higher reward compared to that obtained by choosing cards from the "safe" decks ($100 vs $25, respectively), net losses associated to risky choices are superior to those obtained by selecting cards from the "safe" decks, which actually, on average, yield a $25 net profit.

On the other hand, whilst decks A and C provide high-frequency but low-magnitude penalties (with a ratio of total wins to total losses larger in deck C than deck A), decks B and D provide low-frequency but high-magnitude penalties (with a ratio of total wins to total losses larger in deck D than in deck B). Therefore, profitability of the decks (CD vs. AB) is orthogonalized from punishment frequency/magnitude (BD vs. AC) (Adida et al.,2008).

Participants must complete 100 trials, divided into five blocks of 20 trials. Net score, which is considered as a proxy of decision-making ability, was based on the following formula: number of safe choices minus risky selections [(C+D)-(A+B)], where higher scores are related to better decision-making ability. This index was calculated over the five blocks and also over all choices. The formula [(B+D)-(A+C)] was used to assess sensitivity to punishment (Adida et al,. 2011). Positive values indicate that the individual prefers a low-frequency penalty pattern, whilst negative scores are associated with an inclination towards high-frequency punishment, or in other words, with a low sensitivity to punishment (Adida et al.,2008).

Statistical analysis

Firstly, patients were grouped by means of a data-driven approach to identify neurocognitive profiles concerning IGT performance. Patients' raw scores on decision-making ability [(C+D)-(A+B)], sensitivity to punishment index [(B+D)-(A+C)] and total risky choices (A+B) were standardized to z-scale scores based on the performance of the whole sample.

Ward linkage was chosen as the agglomeration procedure and Euclidean distance was selected to compute similarities between cases. No pre-standardization was required, since all variables were previously standardized (mean=0; SD=1). Later, in order to confirm the number of clusters to be retained, the dendogram was visually inspected. In addition, a discriminant function analysis (DFA) was carried out in order to exam the validity of the obtained clusters. The IGT profiles of the patients in the different clusters were compared using a one-way analysis of variance (ANOVA), with cluster membership as a fixed factor and the three IGT indexes as dependent variables. Furthermore, Tukey post-hoc comparisons were carried out to identify pair-wise differences between groups. To assess potential associations between different IGT groups and sociodemographic, clinical, neuropsychological, and functional variables, we carried out one-way ANOVA or Chi-square tests, followed by a post-hoc comparison when significant main effects were present, as applicable. Statistical significance was set at $p<0.05$. All statistical procedures were performed using SPSS v.23.

RESULTS

Results obtained from hierarchical cluster analysis and data provided by visual inspection of the dendogram indicated that assessed patients were properly grouped, according to IGT performance, into three different clusters: the first cluster included 62 individuals (49.2%), the second one, 44 individuals (34.9%) and the last one, 20 subjects (15.9%). In order to ratify the validity of the three obtained clusters, we carried out a DFA. In this sense, the DFA revealed

the presence of two discriminant functions explaining the 76.5% and the 23.5 % of the variance (Wilks' λ=0.200, χ^2= 197.231, p<0.001; Wilks' λ=0.612, χ^2= 60.140, p<0.001), respectively. Sensitivity to punishment and risky choices contributed most to classify bipolar patients into the different subgroups showing the highest standardized coefficients (0.99 and 0.98, respectively). The 88.9% of original grouped patients were correctly classified with the DFA. Subject grouping into the three clusters are shown in Figure 1.

Comparisons between clusters on IGT performance

The ANOVA analysis indicated that IGT performance as measured by the different indexes differed significantly between the three obtained clusters (see Figure 2). Patients in the first cluster presented the highest rates of risky choices, however they were more prone to select cards from B and D decks, which is consistent with a more conservative punishment sensitivity profile. Concerning decision making ability, patients belonging to this group presented the poorest outcome and showed a non-ascending learning curve (see Figure 3). Despite the fact that patients from cluster 2 generally made more elections from the advantageous decks and showed a moderate steeper learning curve, they presented the highest rates of selection of cards from the A and C decks, which provide the highest penalty frequency rates amongst the three clusters. Patients from cluster 3 obtained the highest net scores, achieving a positive steeper learning curve over the course of the task. This group was also the one who made the largest amount of advantageous choices and presented the highest rates of punishment sensitivity amongst all three groups (see Figure 3).

Comparisons between clusters on sociodemographic, clinical, and functioning

As reported in Table 1, no differences were found regarding sociodemographic, clinical, and pharmacological treatment variables. However, when functional outcomes were compared, some differences were detected pertaining to financial issues and interpersonal relationships FAST scores. In this regard, patients belonging to cluster 2 presented the greatest functional impairment in both domains, especially when compared to patients from cluster 1 ($p=.039$; C1<C2 and $p=.043$; C1<C2, respectively).

Comparison between clusters on neurocognitive measures

Patients from cluster 2 were also found to present the worst cognitive performance on the TMT-B, which is a measure of cognitive flexibility and set shifting, especially when compared to cluster 3 patients ($p=.029$; C2>C3). Likewise, patients belonging to the second cluster also presented higher rates of omissions in the CPT-II tasks ($p=.034$; C2>C3). The same tendency was observed regarding tasks included on the emotional management branch from the MSCEIT, where patients grouped in cluster 2 also underperformed in comparison to cluster 3 patients ($p=.001$; C2>C3). No significant differences between clusters were observed regarding any other assessed neurocognitive variables (see Table 2).

DISCUSSION

To the best of our knowledge, this is the first study intended to identify different profiles on emotional decision-making and reward-processing processes based on the IGT performance in a sizeable euthymic bipolar population. In addition, the study explored the associated clinical, neurocognitive, and functional characteristics. Our results suggest the existence of three discrete patterns: first, our data reveal a cluster which was composed of patients presenting poor decision-making, showing poor and inconsistent patterns of choice that reveal a

decreased learning capacity. Notwithstanding, despite being the group that made more risky choices amongst the three obtained clusters, they presented a pattern of choice consistent with a conservative punishment approach or, in other words, they were more prone to pick cards from the decks with lower frequency-ratios of penalties. The second cluster of patients was mainly characterized by the fact of being less sensitive to punishment, being more prone to pick cards from the decks with high-frequency penalties. Finally, patients belonging to the remaining cluster showed proper decision-making ability, characterized by a steeper learning curve and the achievement of high net scores. Patients from this group also exhibited the highest punishment-sensitive pattern of choice and clearly avoided the selection of cards from decks with high-frequency penalties.

Our results would reinforce the ideas defended by Duek and colleagues whereby each patient has an inherent tendency to react more to either reward or punishment, supporting the existence of an intra-group variability regarding this matter (Duek et al., 2014). However, although two clusters with an opposite punishment sensitivity profile (cluster 2 and 3) presented an adjusted learning ability over the course of the task, it should be remarked that patients presenting higher levels of punishment sensitivity clearly outperformed. Thus, we could conclude that even though a substantial proportion of euthymic bipolar patients learn from both reward and punishment, rates of learning by punishment or negative reinforcement seems to be superior to those resulting from positive rewards in people with bipolar disorder. These results would also comport with findings reported by Duek and colleagues, which indicate that overall learning from punishment was superior to learning from reward as assessed by means of another decision-making task in a group of euthymic bipolar patients (Duek et al., 2014).

While several works have indicated that manic patients show higher sensitivity to reward and depressed ones are more sensitive to punishment (Adida, Jollant, Clark, Besnier, Guillaume,

Kaladjian, Mazzola-Pomietto, Jeanningros, Goodwin, Azorin, and Courtet, 2011;Van der Gucht et al., 2009;van Enkhuizen J. et al., 2014), we were not able to find a similar relationship in our work. Although our sample was constituted entirely by euthymic patients, one could not exclude the possibility that some variables traditionally related to an increased incidence of different type of episodes, such as polarity at first episode and predominant polarity, would be related to a specific punishment sensitivity pattern. However, our data did not reveal any difference between the aforementioned variables and sensitivity to punishment. No differences were found between clusters regarding depressive or manic subsyndromal symptoms. Therefore, in light of our results, the decision-making ability-reward processing profile seems to be independent of the clinical symptoms and other variables related to illness course.

Notwithstanding, it is interesting to point out that approximately the 65% of the assessed sample (62 patients from cluster 1 and 20 from cluster 3) showed an increased sensitivity to punishment even during remission periods. This would be in line with previous works, which defend the idea of an increased sensitivity to punishment among bipolar patients (Minassian et al., 2004;Roiser et al., 2009b).

In regards to the impact of the reward processing profile on illness course, a pattern of a lower sensitivity to punishment seems to negatively impact functional outcome. In our case, the group that showed an increased tendency to choose cards that reported high-frequency penalties (cluster 2) resulted more functionally impaired, especially on financial issues and interpersonal relationships domains. Our findings, therefore, would comport with those reported by Cotrena and colleagues, since they found an association between the IGT performance and functioning, specifically concerning autonomy-related issues, in the most functionally affected group of patients. However, this work explored the impact of clinical and cognitive variables on four resulting clusters based on functioning outcome and quality of life,

and, additionaly, included depressed and remitted patients with diagnosis of both bipolar and major depressive disorder (Cotrena et al., 2016).

In addition to functional impairment, patients from cluster 2 also showed neurocognitive dysfunction. Patients belonging to this cluster achieved the worst performance on tasks assessing attention, showing higher rates of omission errors, and executive function domains, mainly concerning cognitive flexibility and set shifting; the poorer performance is evident especially when compared to patients from cluster 3. Since there is evidence of an interaction between some reward-related issues (reward-based decision-taking and reward anticipation) and neurocognitive performance (Botvinick et al., 2015;Rowe et al., 2008), these findings were not unexpected. Furthermore, is it well-rehearsed that cognitive and reward systems share overlapping neurobiological pathways, among which stand out the dopaminergic system, which in turn is involved in the pathophysiology of bipolar disorder (Cousins et al., 2009).

Additionally, patients from cluster 2 also presented more difficulties in social cognition, specifically on the Emotional Management branch, which assesses the ability to handle their own as well as other's emotions. This finding would be in line with the results from another study where sensitivity to reward bias was associated to MSCEIT performance in a mixed sample of schizophrenic, bipolar patients, and healthy controls (Lewandowski et al., 2016). Nonetheless, they did not find a relationship between reward abnormalities and cognitive performance as measured by the MATRICS Consensus Cognitive Battery (MCCB). Perhaps this lack of association would be due to methodological issues, since our neurocognitive battery, based on the ISBD-Battery for Assessment of Neurocognition (ISBD-BANC) consensus (Yatham et al., 2010), was specifically optimized for being used in bipolar population research and indicated for an accurate detection of cognitive impairment in bipolar disorder. Our results would also reinforce a recent work pointing out the link between MSCEIT performance, neurocognitive outcomes and psychosocial functioning in bipolar patients (Varo et al., 2017).

Thus, in light of our results, one may argue that lower sensitivity to punishment is associated with an impaired neurocognitive performance, specifically on the attentional and executive function domains, which, in turn, could be impacting on social cognition. Maybe low sensibility to punishment impacts the ability to detect and adequately integrate negative feedback emitted during situations of interpersonal communication. The poorer cognitive flexibility observed in this group of patients would jeopardize decision making leading to a low attainment in handling emotional information.

All in all, our results reinforce all those works pointing out that reward processing and cognitive impairment are associated with poorer functioning and higher levels of disability (Green, 2006;Lewandowski et al., 2016). In this sense, among the three analyzed indexes, the presence of lower levels of sensitivity to punishment is the index that seems to have the greatest impact on cognitive and functioning outcomes. Moreover, it should be mentioned that DFA also confirmed its relevance as a strong predictor of group membership. Despite directionality of this relationship could not be reported, it is remarkable that low sensitivity to punishment in bipolar patients would compromise their daily-life functioning.

The present work has some limitations. First, since a considerable proportion of the analyzed sample was recruited from tertiary centers, some participants may represent a more severely affected group of patients. Therefore, generalization of our results should be done carefully. Secondly, further studies with larger samples of bipolar patients are needed in order to replicate our findings. Additionally, bearing in mind the unequal proportion of patients between the three clusters, larger size groups could result in more significant differences regarding the clinical and sociodemographic variables analyzed. Another methodological caveat to consider is that our study was an exploratory analysis with a descriptive purpose, and correction for multiple comparisons was not carried out, which may have increased the false

positive rate in the study. Thirdly, the cross-sectional design of this study does not enable us to determine the directionality of the obtained associations or the stability of the resulting profiles of performance over illness course. Finally, despite all patients were instructed not to take benzodiazepines 24 hours before the neurocognitive assessment, we cannot dismiss the potential negative long-term effect of this medication on neurocognitive performance.

Despite limitations, our data suggest the existence of different profiles of reward processing and decision-making in patients diagnosed with bipolar disorder. Although being relatively independent of the clinical course, the assessment of the aforementioned dimensions should be taken into consideration in early stages of the illness. In this sense, sensitivity to punishment may emerge as a potential marker of poorer outcomes, especially regarding some cognitive and psychosocial functioning domains. The presence of a cognitive pattern characterized by low levels of sensitivity to punishment may guide clinicians in early intervention, especially to treatments aimed to enhance functional outcome as well as different cognitive domains. In this regard, functional remediation would represent a good option. Further studies with larger samples and longitudinal designs are needed in order to confirm our results and to establish the stability of the obtained clusters.

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CHARACTERIZING DECISION-MAKING AND REWARD PROCESSING IN BIPOLAR DISORDER: A CLUSTER ANALYSIS.

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ABSTRACT

The presence of abnormalities in emotional decision-making and reward processing among bipolar patients (BP) has been well rehearsed. These disturbances are not limited to acute ~~illness~~ phases and are common even during remission. In recent years, the existence of discrete cognitive profiles in this psychiatric population has been replicated. However, emotional decision making and reward processing domains have barely been studied. Therefore, our aim was to explore the existence of different profiles on the aforementioned cognitive dimensions in ~~bipolar patients~~ BP.

The sample consisted of 126 euthymic ~~bipolar outpatients~~ BP. Main sociodemographic, clinical, functioning, and neurocognitive variables were gathered. A hierarchical-clustering technique was used to identify discrete neurocognitive profiles based on the performance in the Iowa Gambling Task. Afterward, the resulting clusters were compared using ANOVA or Chi-squared Test, as appropriate.

Evidence for the existence of three different profiles was provided. Cluster 1 was mainly characterized by poor decision ability. Cluster 2 presented the lowest sensitivity to punishment. Finally, cluster 3 presented the best decision-making ability and the highest levels of punishment sensitivity. Comparison between the three clusters indicated that cluster 2 was the most functionally impaired group. The poorest outcomes in attention, executive function domains, and social cognition were also observed within the same group.

In conclusion, similarly to that observed in “cold cognitive” domains, our results suggest the existence of three discrete cognitive profiles concerning emotional decision making and reward processing. Amongst all the indexes explored, low punishment sensitivity emerge as a potential correlate of poorer cognitive and functional outcomes in bipolar disorder.

INTRODUCTION

It has been widely proven that bipolar patients present cognitive impairment even in euthymic periods (Grande et al., 2016). Amongst all domains, attention, verbal memory, and executive function have been pointed out as the most affected areas in this group of patients (Bora et al., 2009;Miskowiak et al., 2017). Despite not being studied as exhaustively as the cognitive domains that make up the so-called "cold cognition", in recent years, there is a growing interest in the study of those domains where emotional processing is involved. Out of all studies, those on affective decision-making as well as reward processing were which led the way on the study on “hot cognitive domains”. These types of studies usually examine how bipolar patients weigh up different alternatives associated with variable degrees of reward and punishment using a variety of paradigms attempting to mimic real-life decision-making processes (Samame, 2013). To date, studies in the field have examined different aspects of reward processing in bipolar patients, including responses to various types of positive stimuli, affective response to rewards, and aspects of decision making or judgments, which target similar regions of the brain. Among all paradigms used, it should be remarked the relevance of the Iowa Gambling Test (IGT) (Bechara et al., 1994) which, indeed, has been recommended by the NIMH RDoC workshop on Positive Valence Systems as a measure of approach motivation (NIMH, 2011). Overall, several studies in this field have consistently reported poorer outcomes on both decision-making abilities as well as response to reward in bipolar patients compared to healthy controls (Adida et al., 2008;Brambilla et al., 2013;Malloy-Diniz et al., 2009;Powers et al., 2013;Roiser et al., 2009a;Strakowski et al., 2009). More specifically, different studies confirm that bipolar patients underperform in the IGT independently of mood state, even during euthymia (Adida et al., 2011;Edge et al., 2013), and have shown that increased risk

taking goes beyond manic states, being also elevated in patients presenting acute depression (Rubinsztein et al., 2006). Concerning sensitivity to punishment, some studies have reported that bipolar patients, in general terms, are more prone to avoid high-frequency penalties options (Adida, Jollant, Clark, Besnier, Guillaume, Kaladjian, Mazzola-Pomietto, Jeanningros, Goodwin, Azorin, and Courtet, 2011;Adida et al., 2015;Powers, Russo, Mahon, Brand, Braga, Malhotra, and Burdick, 2013) even during remission periods. Thus, bipolar disorder is characterized by both impaired reward processing and decision-making ability. Nonetheless, it remains unknown whether these deficits precede illness onset or are a consequence of the disease.

Besides, recent studies agreed that cognitive impairment observed among bipolar population seems to adjust to different profiles of severity. Different independent studies have identified three distinct cognitive profiles among bipolar patients: an intact group, which present a preserved neuropsychological performance; a selectively impaired group, whose neurocognitive performance is only significantly affected in few cognitive domains; and lastly, a global cognitively impaired group (Burdick et al., 2014;Jensen et al., 2016;Jimenez et al., 2017;Lewandowski et al., 2014;Sole et al., 2016;Van Rheenen et al., 2017). Nonetheless, these conclusions raised from studies mostly focused on “cold cognitive” domains, and none of these studies considered the performance on the IGT to carry out their analysis.

Therefore, our goal was to explore the existence of discrete cognitive profile in bipolar population according to their performance in the IGT. We hypothesized that, similar to what happens with the “cold cognitive” domains, heterogeneous profiles involving decision-making ability, risky choices, and punishment sensitivity would exist among bipolar patients, and that different clinical, neurocognitive and functional variables would be linked to each subgroup of patients.

EXPERIMENTAL PROCEDURES

Participants

One-hundred and twenty-six euthymic bipolar outpatients were recruited from the Bipolar Disorder Program of the Hospital Clinic of Barcelona and Mental Health Services from Oviedo, both under the umbrella of the Spanish Research Network on Mental Health (CIBERSAM).

Participants were selected only if they fulfilled the following inclusion criteria: (i) DSM-IV-TR criteria for bipolar I or bipolar II disorder (ii) age over 18 years, (iii) meeting criteria for euthymia for at least three months before inclusion assessed by means of the Hamilton Depression Rating Scale (HDRS)(Ramos-Brieva et al., 1986) and the Young Mania Rating Scale (YMRS) (Colom et al., 2002)(criteria was set out at HDRS≤8 and YMRS ≤6) and (iv) obtaining both written and verbal informed consent from all participants. Exclusion criteria were the presence of (i) intelligence quotient (IQ) lower than 70, (ii) the presence of any medical condition affecting neuropsychological performance, and (iii) electroconvulsive therapy within the past year. Concerning pharmacological treatment, no restrictions were made, including the use of benzodiazepines, in order to capture a representative sample of bipolar population. Nevertheless, all the patients were instructed to not take benzodiazepines 12 hours prior to the neuropsychological assessment. This study was approved by each institution's ethics committees and was carried out in accordance with the ethical principles of the Declaration of Helsinki.

Assessment

Sociodemographic, clinical and functioning variables

All participants were evaluated by means of a semi-structured interview based on the Structured Clinical Interview for DSM Disorders (SCID) in order to collect main sociodemographic and clinical data. Medical records were also reviewed and considered. The

severity of depressive and manic symptomatology was assessed by means of the HDRS and YMRS, respectively.

Level of functioning was gathered through the administration of the Functioning Assessment Short Test (FAST)(Rosa et al., 2007) . This brief ~~hetero~~ interviewer-administered scale, which comprises 24 items, assesses six specific functioning domains: autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationships and leisure time. Higher scores indicate a greater degree of functional impairment, being 72 the highest possible value (Rosa *et al.*2007).

The Barratt Impulsiveness Scale (BIS-11) (Patton et al., 1995) was used to evaluate trait-impulsivity. This self-rated 30-item questionnaire comprises three subscales: attentional-cognitive, motor, and non-planning impulsivity. Scores range from 30 to 120, with higher scores indicating greater impulsivity.

Suicidal ideation and behavior were rated by means of the Columbia Suicide Severity Rating Scale (C-SSRS) (Al-Halabi et al., 2016;Posner et al., 2011). This semi-structured interview assesses four constructs through four subscales: suicidal ideation, intensity of ideation, suicidal behavior and lethality. Suicidal profiles were established as set out in a previous work (Jimenez et al., 2016) as follows: patients who scored less than or equal to 1 at the *Suicidal Ideation* subscale were considered as non-suicidal patients. The remaining patients were in turn grouped into two groups ("history of suicidal ideation" and "history of suicidal ideation and behavior") according whether or not they fulfilled criteria for the Actual Attempt item from the *Suicidal Behavior* Scale.

Neurocognitive assessment

All participants were evaluated using a comprehensive neuropsychological battery based on a wide review of the existing literature in the field, in order to assess different cognitive domain performance.

- The estimated IQ was calculated based on the performance on the Vocabulary subtest from the Wechsler Adult Intelligence Scale (WAIS-III) (Wechsler D., 1997).
- The Processing speed domain comprised two subtests of the WAIS-III: the Symbol Search and the Digit-symbol Coding subtests (Wechsler D., 1997), the Trail Making Test-Part A (TMT-A) (Reitan.R.M., 1958), and the Categorical (Animal Naming) and the Phonemic (F-A-S) components of the Controlled Oral Word Association Test (COWAT) (Benton et al., 1976).
- Three subtest from the WAIS-III: Arithmetic, Digits, and Letter-Number sequencing composed the Working memory index (WM) (Wechsler D., 1997).
- The California Verbal Learning Test (CVLT) (Delis et al., 1987) was used to test Verbal Learning and Memory performance.
- Visual memory and learning was assessed through the Rey Osterrieth Complex Figure (ROCF) (Rey, 1997).
- The computerized version of the Continous Performance Test (CPT-II)(Conners, 2002) was used to explore Attention.
- The executive functions were measured by means of different tests examining response inhibition, set shifting and planning, specifically, the Stroop Color-Word Interference Test (Golden, 1978), the computerized Wisconsin Card Sorting Test (WSCT)(Heaton, 1981) and Trail Making Test-Part B (TMT-B) (Reitan.R.M., 1958).
- The Mayer–Salovey–Caruso Emotional Intelligence Test, version 2.0 (MSCEIT) (Brackett et al., 2006;Extremera et al., 2006) ~~were tested~~ was used to evaluate Social Cognition, more specifically Emotional Intelligence.

Decision-making and reward processing were assessed by means of the computerized version of the IGT (Bechara et al., 1994). In this task, participants are asked to choose cards from four different decks (A, B, C, and D). Each card selected results always in a gain and, for some cards, also a loss. The goal of the task is to earn as much money as possible.

On the one hand, ~~T~~ there are two "risky" decks (A and B) and two "safe" decks (C and D). Despite cards from the "risky" decks imply, on average, a higher reward compared to that obtained by choosing cards from the "safe" decks ($100 vs $25, respectively), net losses associated to risky choices are superior to those obtained by selecting cards from the "safe" decks, which actually, on average, yield a $25 net profit.

On the other hand, whilst decks A and C provide high-frequency but low-magnitude penalties (with a ratio of total wins to total losses larger in deck C than deck A), decks B and D provide low-frequency but high-magnitude penalties (with a ratio of total wins to total losses larger in deck D than in deck B). Therefore, profitability of the decks (CD vs. AB) is orthogonalized from punishment frequency/magnitude (BD vs. AC) (Adida et al.,2008).

Participants must complete 100 trials, divided into five blocks of 20 trials. Net score, which is considered as a proxy of decision-making ability, was based on the following formula: number of safe choices minus risky selections [(C+D)-(A+B)], where higher scores are related to better decision-making ability. This index was calculated over the five blocks and also over all choices. The formula [(B+D)-(A+C)] was used to assess sensitivity to punishment (Adida et al,. 2011). Positive values indicate that the individual prefers a low-frequency penalty pattern, whilst negative scores are associated with an inclination towards high-frequency punishment, or in other words, with a low sensitivity to punishment (Adida et al.,2008).

Statistical analysis

Firstly, patients were grouped by means of a data-driven approach to identify neurocognitive profiles concerning IGT performance. Patients' raw scores on decision-making ability [(C+D)-(A+B)], sensitivity to punishment index [(B+D)-(A+C)] and total risky choices (A+B) were standardized to z-scale scores based on the performance of the whole sample.

Ward linkage was chosen as the agglomeration procedure and Euclidean distance was selected to compute similarities between cases. No pre-standardization was required, since all variables were previously standardized (mean=0; SD=1). Later, in order to confirm the number of clusters to be retained, the dendogram was visually inspected. In addition, a discriminant function analysis (DFA) was carried out in order to exam the validity of the obtained clusters. The IGT profiles of the patients in the different clusters were compared using a one-way analysis of variance (ANOVA), with cluster membership as a fixed factor and the three IGT indexes as dependent variables. Furthermore, Tukey post-hoc comparisons were carried out to identify pair-wise differences between groups. To assess potential associations between different IGT groups and sociodemographic, clinical, neuropsychological, and functional variables, we carried out one-way ANOVA or Chi-square tests, followed by a post-hoc comparison when significant main effects were present, as applicable. Statistical significance was set at $p<0.05$. All statistical procedures were performed using SPSS v.23.

RESULTS

Results obtained from hierarchical cluster analysis and data provided by visual inspection of the dendogram indicated that assessed patients were properly grouped, according to IGT performance, into three different clusters: the first cluster included 62 individuals (49.2%), the second one, 44 individuals (34.9%) and the last one, 20 subjects (15.9%). In order to ratify the validity of the three obtained clusters, we carried out a DFA. In this sense, the DFA revealed

the presence of two discriminant functions explaining the 76.5% and the 23.5 % of the variance (Wilks' λ=0.200, χ^2= 197.231, p<0.001; Wilks' λ=0.612, χ^2= 60.140, p<0.001), respectively. Sensitivity to punishment and risky choices contributed most to classify bipolar patients into the different subgroups showing the highest standardized coefficients (0.99 and 0.98, respectively). The 88.9% of original grouped patients were correctly classified with the DFA. Subject grouping into the three clusters are shown in Figure 1.

Comparisons between clusters on IGT performance

The ANOVA analysis indicated that IGT performance as measured by the different indexes differed significantly between the three obtained clusters (see Figure 2). Patients in the first cluster presented the highest rates of risky choices, however they were more prone to select cards from B and D decks, which is consistent with a more conservative punishment sensitivity profile. Concerning decision making ability, patients belonging to this group presented the poorest outcome and showed a non-ascending learning curve (see Figure 3). Despite the fact that patients from cluster 2 generally made more elections from the advantageous decks and showed a moderate steeper learning curve, they presented the highest rates of selection of cards from the A and C decks, which provide the highest penalty frequency rates amongst the three clusters. Patients from cluster 3 obtained the highest net scores, achieving a positive steeper learning curve over the course of the task. This group was also the one who made the largest amount of advantageous choices and presented the highest rates of punishment sensitivity amongst all three groups (see Figure 3).

Comparisons between clusters on sociodemographic, clinical, and functioning

As reported in Table 1, no differences were found regarding sociodemographic, clinical, and pharmacological treatment variables. However, when functional outcomes were compared, some differences were detected pertaining to financial issues and interpersonal relationships FAST scores. In this regard, patients belonging to cluster 2 presented the greatest functional impairment in both domains, especially when compared to patients from cluster 1 (p=.039; C1<C2 and p=.043; C1<C2, respectively).

Comparison between clusters on neurocognitive measures

Patients from cluster 2 were also found to present the worst cognitive performance on the TMT-B, which is a measure of cognitive flexibility and set shifting, especially when compared to cluster 3 patients (p=.029; C2>C3). Likewise, patients belonging to the second cluster also presented higher rates of omissions in the CPT-II tasks (p=.034; C2>C3). The same tendency was observed regarding tasks included on the emotional management branch from the MSCEIT, where patients grouped in cluster 2 also underperformed in comparison to cluster 3 patients (p=.001; C2>C3). No significant differences between clusters were observed regarding any other assessed neurocognitive variables (see Table 2).

DISCUSSION

To the best of our knowledge, this is the first study intended to identify different profiles on emotional decision-making and reward-processing processes based on the IGT performance in a sizeable euthymic bipolar population. In addition, the study explored the associated clinical, neurocognitive, and functional characteristics. Our results suggest the existence of three discrete patterns: first, our data reveal a cluster which was composed of patients presenting poor decision-making, showing poor and inconsistent patterns of choice that reveal a

decreased learning capacity. Notwithstanding, despite being the group that made more risky choices amongst the three obtained clusters, they presented a pattern of choice consistent with a conservative punishment approach or, in other words, they were more prone to pick cards from the decks with lower frequency-ratios of penalties. The second cluster of patients was mainly characterized by the fact of being less sensitive to punishment, being more prone to pick cards from the decks with high-frequency penalties. Finally, patients belonging to the remaining cluster showed proper decision-making ability, characterized by a steeper learning curve and the achievement of high net scores. Patients from this group also exhibited the highest punishment-sensitive pattern of choice and clearly avoided the selection of cards from decks with high-frequency penalties.

Our results would reinforce the ideas defended by Duek and colleagues whereby each patient has an inherent tendency to react more to either reward or punishment, supporting the existence of an intra-group variability regarding this matter (Duek et al., 2014). However, although two clusters with an opposite punishment sensitivity profile (cluster 2 and 3) presented an adjusted learning ability over the course of the task, it should be remarked that patients presenting higher levels of punishment sensitivity clearly outperformed. Thus, we could conclude that even though a substantial proportion of euthymic bipolar patients learn from both reward and punishment, rates of learning by punishment or negative reinforcement seems to be superior to those resulting from positive rewards in people with bipolar disorder. These results would also comport with findings reported by Duek and colleagues, which indicate that overall learning from punishment was superior to learning from reward as assessed by means of another decision-making task in a group of euthymic bipolar patients (Duek et al., 2014).

While several works have indicated that manic patients show higher sensitivity to reward and depressed ones are more sensitive to punishment (Adida, Jollant, Clark, Besnier, Guillaume,

Kaladjian, Mazzola-Pomietto, Jeanningros, Goodwin, Azorin, and Courtet, 2011;Van der Gucht et al., 2009;van Enkhuizen J. et al., 2014), we were not able to find a similar relationship in our work. Although our sample was constituted entirely by euthymic patients, one could not exclude the possibility that some variables traditionally related to an increased incidence of different type of episodes, such as polarity at first episode and predominant polarity, would be related to a specific punishment sensitivity pattern. However, our data did not reveal any difference between the aforementioned variables and sensitivity to punishment. No differences were found between clusters regarding depressive or manic subsyndromal symptoms. Therefore, in light of our results, the decision-making ability-reward processing profile seems to be independent of the clinical symptoms and other variables related to illness course.

Notwithstanding, it is interesting to point out that approximately the 65% of the assessed sample (62 patients from cluster 1 and 20 from cluster 3) showed an increased sensitivity to punishment even during remission periods. This would be in line with previous works, which defend the idea of an increased sensitivity to punishment among bipolar patients (Minassian et al., 2004;Roiser et al., 2009b).

In regards to the impact of the reward processing profile on illness course, a pattern of a lower sensitivity to punishment seems to negatively impact functional outcome. In our case, the group that showed an increased tendency to choose cards that reported high-frequency penalties (cluster 2) resulted more functionally impaired, especially on financial issues and interpersonal relationships domains. Our findings, therefore, would comport with those reported by Cotrena and colleagues, since they found an association between the IGT performance and functioning, specifically concerning autonomy-related issues, in the most functionally affected group of patients. However, this work explored the impact of clinical and cognitive variables on four resulting clusters based on functioning outcome and quality of life,

and, additionaly, included depressed and remitted patients with diagnosis of both bipolar and major depressive disorder (Cotrena et al., 2016).

In addition to functional impairment, patients from cluster 2 also showed neurocognitive dysfunction. Patients belonging to this cluster achieved the worst performance on tasks assessing attention, showing higher rates of omission errors, and executive function domains, mainly concerning cognitive flexibility and set shifting; the poorer performance is evident especially when compared to patients from cluster 3. Since there is evidence of an interaction between some reward-related issues (reward-based decision-taking and reward anticipation) and neurocognitive performance (Botvinick et al., 2015;Rowe et al., 2008), these findings were not unexpected. Furthermore, is it well-rehearsed that cognitive and reward systems share overlapping neurobiological pathways, among which stand out the dopaminergic system, which in turn is involved in the pathophysiology of bipolar disorder (Cousins et al., 2009).

Additionally, patients from cluster 2 also presented more difficulties in social cognition, specifically on the Emotional Management branch, which assesses the ability to handle their own as well as other's emotions. This finding would be in line with the results from another study where sensitivity to reward bias was associated to MSCEIT performance in a mixed sample of schizophrenic, bipolar patients, and healthy controls (Lewandowski et al., 2016). Nonetheless, they did not find a relationship between reward abnormalities and cognitive performance as measured by the MATRICS Consensus Cognitive Battery (MCCB). Perhaps this lack of association would be due to methodological issues, since our neurocognitive battery, based on the ISBD-Battery for Assessment of Neurocognition (ISBD-BANC) consensus (Yatham et al., 2010), was specifically optimized for being used in bipolar population research and indicated for an accurate detection of cognitive impairment in bipolar disorder. Our results would also reinforce a recent work pointing out the link between MSCEIT performance, neurocognitive outcomes and psychosocial functioning in bipolar patients (Varo et al., 2017).

Thus, in light of our results, one may argue that lower sensitivity to punishment is associated with an impaired neurocognitive performance, specifically on the attentional and executive function domains, which, in turn, could be impacting on social cognition. Maybe low sensibility to punishment impacts the ability to detect and adequately integrate negative feedback emitted during situations of interpersonal communication. The poorer cognitive flexibility observed in this group of patients would jeopardize decision making leading to a low attainment in handling emotional information.

All in all, our results reinforce all those works pointing out that reward processing and cognitive impairment are associated with poorer functioning and higher levels of disability (Green, 2006;Lewandowski et al., 2016). In this sense, among the three analyzed indexes, the presence of lower levels of sensitivity to punishment is the index that seems to have the greatest impact on cognitive and functioning outcomes. Moreover, it should be mentioned that DFA also confirmed its relevance as a strong predictor of group membership. Despite directionality of this relationship could not be reported, it is remarkable that low sensitivity to punishment in bipolar patients would compromise their daily-life functioning.

The present work has some limitations. First, since a considerable proportion of the analyzed sample was recruited from tertiary centers, some participants may represent a more severely affected group of patients. Therefore, generalization of our results should be done carefully. Secondly, further studies with larger samples of bipolar patients are needed in order to replicate our findings. Additionally, bearing in mind the unequal proportion of patients between the three clusters, larger size groups could result in more significant differences regarding the clinical and sociodemographic variables analyzed. Another methodological caveat to consider is that our study was an exploratory analysis with a descriptive purpose, and correction for multiple comparisons was not carried out, which may have increased the false

positive rate in the study. Thirdly, the cross-sectional design of this study does not enable us to determine the directionality of the obtained associations or the stability of the ~~obtained~~ resulting profiles of performance over illness course. Finally, despite all patients were instructed not to take benzodiazepines 24 hours before the neurocognitive assessment, we cannot dismiss the potential negative long-term effect of this medication on neurocognitive performance.

Despite limitations, our data suggest the existence of different profiles of reward processing and decision-making in patients diagnosed with bipolar disorder. Although being relatively independent of the clinical course, the assessment of the aforementioned dimensions should be taken into consideration in early stages of the illness. In this sense, sensitivity to punishment may emerge as a potential marker of poorer outcomes, especially regarding some cognitive and psychosocial functioning domains. The presence of a cognitive pattern characterized by low levels of sensitivity to punishment may guide clinicians in early intervention, especially to treatments aimed to enhance functional outcome as well as different cognitive domains. In this regard, functional remediation would represent a good option. Further studies with larger samples and longitudinal designs are needed in order to confirm our results and to establish the stability of the obtained clusters.

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Table 1

VARIABLES	*CLUSTER GROUPS*			*Statistic*	*p*	*Post-hoc*		
	Cluster 1(C1)	*Cluster 2(C2)*	*Cluster 3(C3)*					
QUANTITATIVE	*N=62*	*N=44*	*N=20*					
	Mean(SD)	*Mean(SD)*	*Mean(SD)*			**C1 vs C2**	**C2 vs C3**	**C1 vs C3**
Age	49.34 (10.338)	48.30(13.107)	44.30(9.761)	1.506	.226			
Illness duration (y)	21.94(9.724)	20.65(10.413)	19.35(10.189)	0.561	.572			
Years of education	14.03(4.534)	13.75(4.144)	13.85(3.468)	0.059	.943			
Age at onset (y)	26.84(9.315)	27.14(11.230)	24.50(7.944)	0.539	.585			
Number of hospitalization	2.5(2.425)	3.05(3.618)	2.05(2.259)	1.703	.186			
Age at 1st admission(y)	34.69(12.885)	29.53(11.034)	33.57(8.244)	1.846	.164			
Number of episodes								
Manic	2.32(4.356)	3.80(5.147)	1.80(2.118)	2.000	.140			
Depressive	9.48(14.173)	7.11(8.082)	5.63(4.166)	1.094	.338			
Hypomanic	4.86(11.786)	3.61(7.098)	4.21(5.381)	0.220	.803			
Mixed	0.83(1.440)	0.52(1.705)	1.63(3.166)	2.291	.106			
FAST								
Autonomy	2.69(2.513)	3.49(3.348)	2.55(2.089)	1.282	.281			
Occupational	9.63(6.410)	8.84(6.799)	8.65(6.604)	0.267	.766			
Cognitive	5.60(3.499)	5.79(3.783)	5.65(3.801)	0.036	.964			
Finance	0.84(1.428)	1.65(2.022)	1.35(1.424)	3.152	**.046**	**.039**	.780	.455
Interpersonal relationship	4.08(3.536)	5.86(4.257)	3.75(2.673)	3.650	**.029**	**.043**	.091	.935
Leisure time	2.31(2.013)	2.30(2.199)	1.65(1.694)	0.870	.421			
Total	25.19(13.778)	28.33(17.334)	23.10(13.992)	0.963	.385			
BIS-11								
Attentional- cognitive	18.57(3.714)	18.93(3.439)	20.22(4.223)	1.373	.258			
Motor	21.03(4.816)	22.29(4.629)	21.00(5.466)	0.911	.405			
Non-planned	23.93(5.143)	24.57(5.356)	25.94(4.193)	1.087	.341			
Total	63.74(10.683)	65.79(10.767)	67.17(9.829)	0.902	.409			
YMRS	1.82(1.971)	1.80(2.007)	2.20(1.881)	0.330	.720			
HDRS	4.19(2.566)	3.89(2.634)	4.20(2.726)	0.200	.819			
No. Suicidal attempts	0.85(2.151)	0.61(1.185)	0.60(1.095)	0.312	.732			
QUALITATIVE	*N(%)*	*N(%)*	*N(%)*					
Gender (male)	22(35.5)	17(38.6)	13(65)	5.629	.060			
Occupation (Not working)	43(69.4)	28(68.3)	11(55)	1.475	.478			

Marital Status (Not married)	38(61.3)	31(70.5)	11(55)	1.672	.433			
Diagnosis (BD I)	43(69.4)	34(77.3)	15(75)	0.866	.648			
Family history of psychiatric disease	52(83.9)	29(65.9)	16(80)	4.808	.090			
Family history of affective disease	47(75.8)	33(75)	17(85)	0.872	.647			
Family history of completed suicide	13(21)	9(20.5)	5(25)	0.184	.912			
1st episode polarity (depression)	43(69.4)	22(51.2)	14(70)	10.046	.123			
Predominant polarity				7.065	.132			
(Hipo)Manic	11(17.7)	10(27.7)	2(10)					
Depressive	21(33.9)	6(13.6)	5(25)					
Not specified	30(48.4)	28(63.6)	13(65)					
Axis I comorbidity	11(17.7)	4(9.1)	3(15)	1.583	.453			
Axis II comorbidity	11(17.7)	8(18.2)	4(20)	0.052	.974			
Axis III comorbidity	25(41)	15(34.1)	8(40)	0.539	.764			
Lifetime rapid cycling	12(19.4)	7(15.9)	6(30)	1.735	.420			
Lifetime psychotic features	38(61.3)	30(68.2)	13(65)	0.538	.764			
Lifetime atypical symptoms	29(46.8)	17(38.6)	12(60)	2.553	.279			
Lifetime consume								
Alcohol	47(75.8)	36(81.8)	20(100)	5.932	.052			
Cannabis	31(50)	22(50)	11(55)	0.168	.919			
Cocaine	15(24.2)	6(13.6)	6(30)	2.741	.254			
Current medication								
Lithium	44(71)	22(50)	13(65)	4.892	.087			
Other mood stabilizers	30(48.4)	26(59.1)	13(65)	2.196	.334			
Antipsychotics	40(65.5)	30(68.2)	17(85)	2.993	.224			
Antidepressants	27(43.5)	17(38.6)	9(45)	0.339	.844			
Benzodiazepines	31(50)	19(43.2)	8(40)	0.830	.660			
Suicidal profile				1.882	.757			
Non suicidal	21(33.9)	20(45.5)	7(35)					
Suicidal Ideators	23(37.1)	12(27.3)	8(40)					
Suicidal attempters	18(29)	12(27.3)	5(25)					

Table 1. Comparisons of sociodemographic, clinical and functioning variables among the three different clusters

Bold text in the table indicates significant values.
BDI, bipolar disorder type 1; SD, standard deviation; FAST, Functioning Assessment Short Test; BIS-11,Barratt Impulsiveness Scale; YMRS, Young Mania Rating Scale; HDRS, Hamilton Depression Rating Scale.

Table 2

	Cluster 1(C1)	***Cluster 2(C2)***	***Cluster 3(C3)***	***Statistic***	***P value***	***Post-Hoc***		
	N=62	***N=44***	***N=20***					
	Mean(SD)	***Mean(SD)***	***Mean(SD)***			**C1 vs C2**	**C2 vs C3**	**C1 vs C3**
Estimated IQ								
Vocabulary (WAIS-III)	109.05 (11.335)	110.23(12.908)	111.00(12.312)	0.238	.789			
Processing Speed								
Digit-Symbol Coding (WAIS-III)	28.47(20.716)	25.63(11.429)	27.75(8.039)	0.385	.681			
F-A-S (COWAT)	34.30(10.944)	33.40(10.929)	36.05(13.725)	0.369	.692			
Animal Naming (COWAT)	18.77(4.897)	16.77 (4.961)	18.20(4.708)	2.118	.125			
TMT-A	41.24(25.699)	42.70(22.875)	34.50(11.812)	0.905	.407			
Working Memory								
Arithmetic (WAIS-III)	10.97(3.773)	11.00(3.916)	12.25(3.810)	0.921	.401			
Digits (WAIS-III)	13.51(3.319)	13.05(3.352)	15.05(4.097)	2.319	.103			
Letter-Number sequencing (WAIS-III)	8.71(2.436)	8.47(2.789)	9.45(3.379)	0.896	.411			
Verbal Learning and Memory								
List A (total) (CVLT)	49.76(13.790)	46.52(14.144)	49.50(16.869)	0.658	.520			
Free short recall (CVLT)	10.79(3.660)	9.29(4.068)	11.55(3.940)	2.949	.056			
Cued short recall (CVLT)	11.83(3.325)	10.67(3.310)	12.25(3.177)	2.146	.122			
Free delayed recall (CVLT)	11.30(3.854)	9.88(3.890)	11.80(3.915)	2.289	.106			
Cued delayed recall (CVLT)	11.61(3.609)	10.88(3.329)	12.65(3.313)	1.779	.170			
Visual Memory								
Recall (ROCF)	18.63(6.810)	17.30(6.501)	20.27(6.996)	0.815	.447			
Executive Function								
Number of Categories (WSCT)	3.97(2.197)	4.14(2.215)	4.70(1.838)	0.871	.421			
Perseverative errors (WSCT)	21.32(16.666)	21.63(17.407)	18.90(15.838)	0.197	.822			
Interference (SCWT)	1.11(8.940)	1.81(7.159)	4.40(6.999)	1.251	.290			
TMT-B	110.98(64.376)	140.79(132.340)	76.45(34.686)	3.526	**.033**	.240	**.029**	.315
Attention								
Omissions (CPT-II)	11.83(15.263)	18.57(24.813)	5.90(8.837)	3.513	**.033**	.169	**.034**	.429
Hit Reaction Time (CPT-II)	463.93(78.442)	501.51(147.57)	453.16(63.793)	2.071	.131			
Hit Reaction Time SE (CPT-II)	8.90(5.642)	12.10(11.557)	7.72(3.836)	2.772	.067			
Social Cognition								
Emotional Perception (MSCEIT)	102.05(12.776)	103.83(15.559)	102.59(13.879)	0.194	.824			
Emotional Facilitation (MSCEIT)	98.51(10.912)	96.80(12.584)	99.53(11.614)	0.408	.666			
Emotional Understanding (MSCEIT)	98.02(11.443)	96.83(13.975)	101.83(14.239)	0.962	.385			
Emotional Management (MSCEIT)	104.34(12.707)	98.41(13.295)	112.47(15.541)	6.910	**.001**	.083	**.001**	.076

Table 2. Comparisons of neurocognitive variables among the three different clusters.

Bold text in the table indicates significant values.

IQ, Intelligence Quotient; WAIS-III, Weschler Adult Intelligence Scale; COWAT, Controlled Oral Word Association Test; TMT, Trail Making Test; CVLT, California Verbal Learning Test; ROCF, Rey Osterrieth Complex Figure; WSCT, Wisconsin Card Sorting Test; CPT-II, Continous Performance Test; MSCEIT, Mayer–Salovey–Caruso Emotional Intelligence Test.

Figure 1

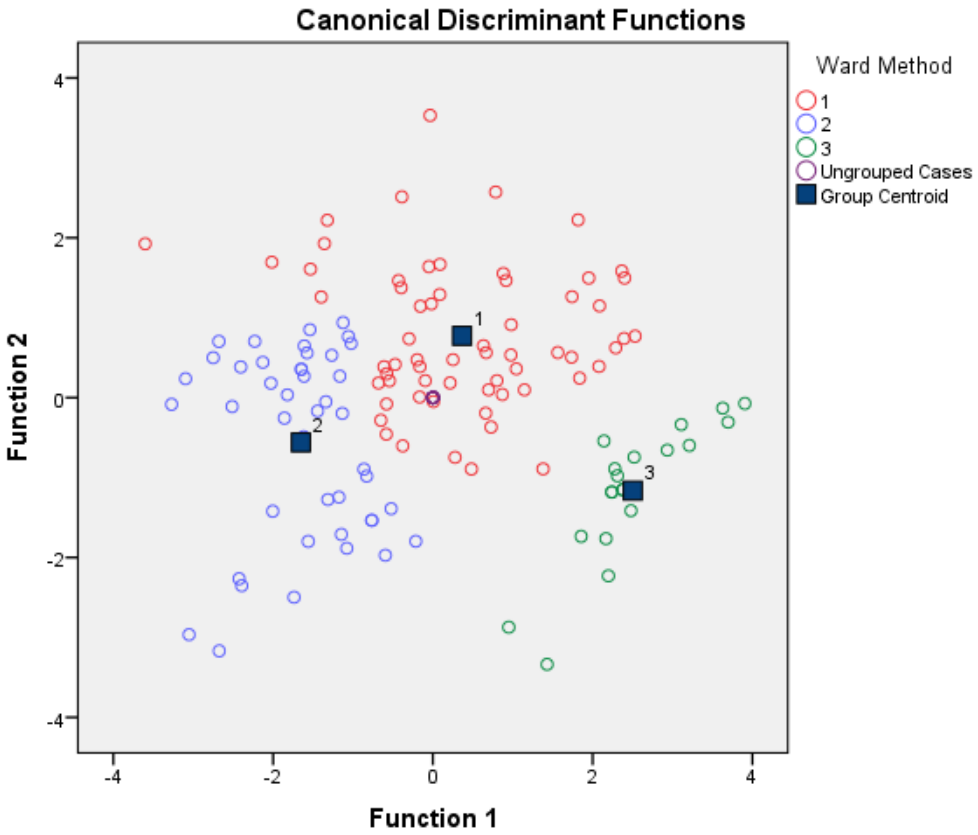

Figure 1. Graphical agglomeration of bipolar participants using discriminant function analysis. The figure represents the agglomeration subjects using the three resulting clusters from the hierarchical cluster analysis. Centroids represent the mean score for each group.

Figure 3

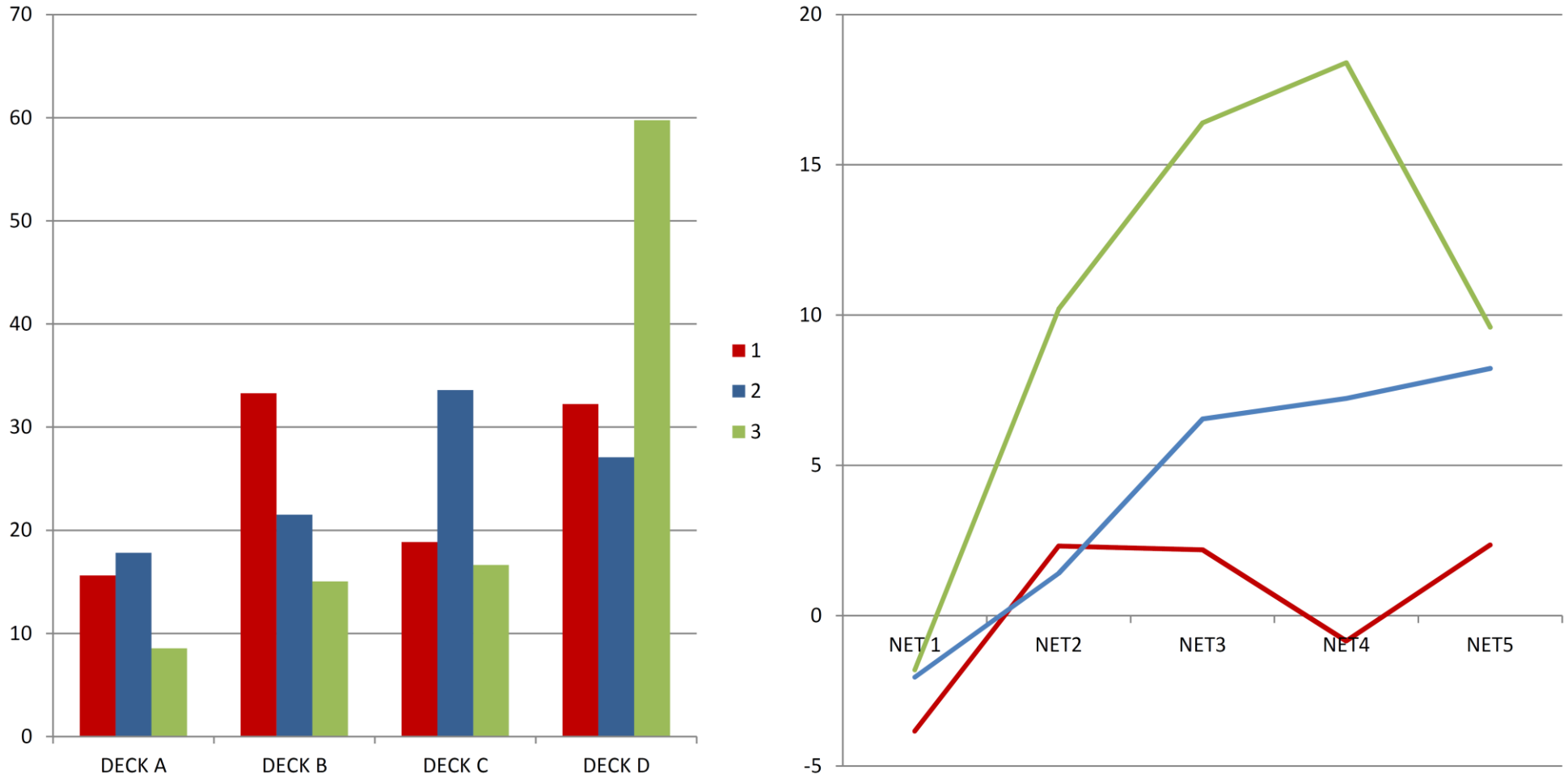

Figure 3. Cards selected from each deck (left) and net score evolution (right) among the three obtained clústers.

Figure 2

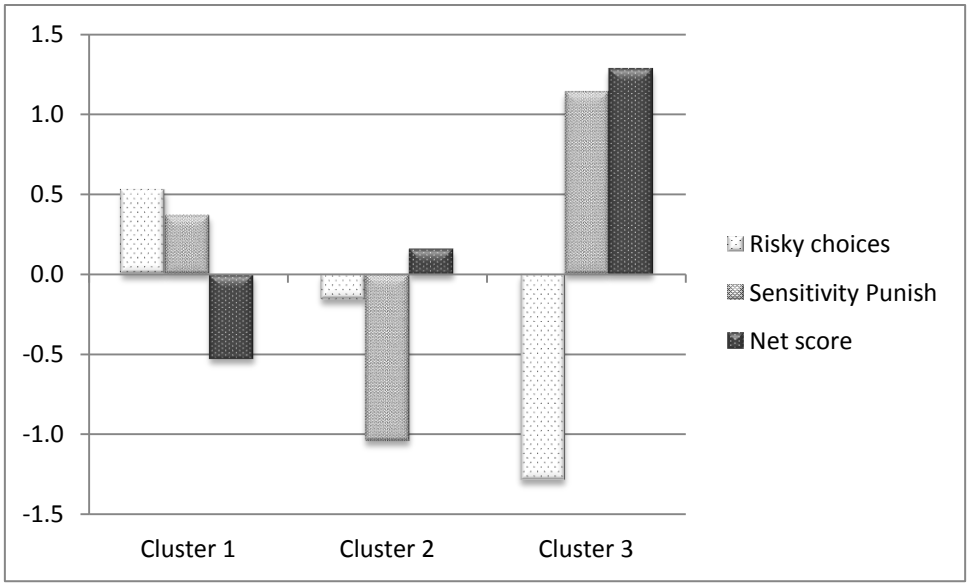

Figure 2 . IGT indexes z-scores amongst the three clusters.

***Role of the Funding Source**

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Contributors

All authors contributed to and have approved the final manuscript.

***Conflict of Interest**

Conflict of Interest

Dr. Antoni Benabarre has received research grants and served as a speaker for the following companies: Grants: Janssen-Cilag and Pfizer. Speaker: Bristol-Myers-Squibb, Eli Lilly, Glaxo-Smith-Kline and Janssen-Cilag.

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