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IDENTIFYING SOCIAL COGNITION SUBGROUPS IN EUTHYMIC PATIENTS WITH BIPOLAR DISORDER: A CLUSTER ANALYTICAL APPROACH

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Abstract:	Background : Bipolar Disorder (BD) is associated with social cognition (SC) impairments even during remission periods although a large heterogeneity has been described. Our aim was to explore the existence of different profiles on SC in patients with BD, and further explore the potential impact of distinct variables on SC. Methods : Hierarchical cluster analysis was conducted using three SC domains (Theory of Mind (ToM), Emotional Intelligence (EI) and Attributional Bias (AB)). The sample comprised of 131 individuals, 71 patients with BD and 60 healthy control subjects who were compared in terms of SC performance, demographic, clinical and neurocognitive variables. A logistic regression model was used to estimate the effect of SC associated risk factors. Results: A two-cluster solution was identified with an adjusted performance group (N=48, 67.6%) and a low performance group (N=23, 32.4%) with mild deficits in ToM and AB domains and with moderate difficulties in E I. Patients with low SC performance were mostly males, showed lower estimated IQ, higher subthreshold depressive symptoms, longer illness duration, and poorer visual memory and attention.

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ABSTRACT

Background: Bipolar Disorder (BD) is associated with social cognition (SC) impairments even during remission periods although a large heterogeneity has been described. Our aim was to explore the existence of different profiles on SC in patients with BD, and further explore the potential impact of distinct variables on SC.

Methods: Hierarchical cluster analysis was conducted using three SC domains (Theory of Mind (ToM), Emotional Intelligence (EI) and Attributional Bias (AB)). The sample comprised of 131 individuals, 71 patients with BD and 60 healthy control subjects who were compared in terms of SC performance, demographic, clinical and neurocognitive variables. A logistic regression model was used to estimate the effect of SC associated risk factors.

Results: A two-cluster solution was identified with an adjusted performance group (N=48, 67.6%) and a low performance group (N=23, 32.4%) with mild deficits in ToM and AB domains and with moderate difficulties in EI. Patients with low SC performance were mostly males, showed lower estimated IQ, higher subthreshold depressive symptoms, longer illness duration, and poorer visual memory and attention. Low estimated IQ (OR=0.920; 95%CI=0.863-0.981), male gender (OR=5.661; 95%CI=1.473–21.762) and longer illness duration (OR=1.085; 95%CI=1.006–1.171) contributed the most to the patients clustering. The model explained up to 35% of the variance in SC performance.

Conclusions: Our results confirmed the existence of two discrete profiles of SC among BD. Nearly two thirds of patients exhibited adjusted social cognitive abilities. Longer illness duration, male gender and lower estimated IQ were associated with low SC performance.

Keywords: Social cognition, bipolar disorders, cluster analysis, Theory of Mind, Emotional Intelligence, Attributional Bias.

INTRODUCTION

In recent years, social cognition (SC) has emerged as a matter of concern in bipolar disorder (BD) research. SC is a multifaceted construct that encompasses a complex set of mental processes including perceiving, interpreting, and generating responses to the intentions, dispositions, and behaviors of others that underlies social interactions and that enable successful and adaptive behavior in a social context (Harvey & Penn, 2010). It involves four core domains including the Emotional Intelligence, Theory of Mind (ToM), Attributional Bias, Social Perception and Knowledge. Specifically, ToM is the ability to comprehend and represent mental states of others, including the inference of intentions, dispositions, and/or beliefs. Next, the ability to share experiences and emotions of others, as well as the capacity to regulate one's emotional responses to others is known as Emotional Intelligence (EI). The Attributional Bias (AB) refers to the way in which individuals explain or reason of the causes of social events or interactions. Finally, the ability to decode and interpret social cues in others is called Social Perception and Knowledge (Green et al., 2008; Sergi et al., 2007).

Social cognitive deficits have been identified in patients with BD, particularly in ToM, emotional intelligence and attributional bias domains (Samamé, 2013). Moreover, these deficits appear even during remission periods (Samamé et al., 2015) and could be present at early stages of the disorder and also among unaffected relatives of patients with BD (Emre Bora & Özerdem, 2017; Kjærstad et al., 2019). These data suggests that SC deficits might represent a trait marker of the illness (Meluken et al., 2019; K. W. Miskowiak et al., 2018; Kamilla W. Miskowiak et al., 2017) and not simply a result of medication side-effects or clinical episodes. However, evidence is still inconclusive as other studies indicate that patients with BD might actually present a quite preserved SC performance, or might have some impairment in only a few SC domains (Burdick et al., 2014; R. S. C. Lee et al., 2015; Sperry et al., 2015; Tamsyn E Van Rheenen & Rossell, 2014; Varo et al., 2017).

Recent cluster analysis studies indicate that neurocognitive performance in patients with BD is heterogeneous. Several studies have identified discrete neurocognitive subgroups in remitted patients with BD (Burdick et al., 2014; Jensen et al., 2016; Esther Jiménez et al., 2017; Lewandowski et al., 2014; Lima et al., 2019; Russo et al., 2017; Solé et al., 2016; T. E. Van Rheenen et al., 2017). These conclusions were assumed from studies mostly focused on neurocognitive domains and none of them has considered the performance using a comprehensive battery of tests covering different facets of SC. Even though, these data suggest that a gradation of severity in SC performance among patients with BD may exist.

As far as we know, there is only one study published by authors from our research team that aimed to examine variability of the emotional intelligence domain (Varo et al., 2017). In this study, a large euthymic BD sample was divided into three subgroups according to normative data and resulting into three groups: average, above or below normative means. Using this method, it was found out that 19% of the sample performed better than the normative population, 69% presented an adjusted emotional intelligence performance. Only 12% of patients with BD were considered to present a low-range emotional intelligence, showing poorer cognitive, clinical and functional outcome scores. However, no previously published studies examining the variability of different SC domains in patients with BD have been published so far. To understand to what extent the specific domains of SC performance are impaired in patients with BD and evaluate whether subjects could be categorized into discrete profiles may aid to expand the knowledge regarding the neural underpinnings and etiology of SC deficits in BD (Russo et al., 2017).

The main aim of this study was to examine the existence of discrete SC profiles in a sample of euthymic patients with BD using a data-driven approach. We focused on three social cognitive subdomains —ToM, emotional intelligence and attributional bias — that have received much attention in BD. Secondly, we evaluated whether participants with different profiles differed in

terms of demographic, clinical and neuropsychological variables and evaluated their contribution to SC performance. We hypothesized that heterogeneous SC profiles would exist among patients with BD, and that patients with a worse SC profile would be characterized by a poorer clinical course and exhibit a greater cognitive impairment.

METHODS

Participants

Seventy-one euthymic outpatients with BD were recruited from the Bipolar and Depressive Disorders Unit of the Hospital Clinic of Barcelona under the umbrella of the Spanish Research Network on Mental Health (CIBERSAM) (Salagre et al., 2019).

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 and 65 years and (iii) euthymia defined as a score ≤8 on the Hamilton Depression Rating Scale (HDRS) (Hamilton, 1967; Ramos-Brieva & Cordero-Villafafila, 1988) and ≤6 on the Young Mania Rating Scale (YMRS) (Colom et al., 2002; Young et al., 1978) of at least the 3 months before the inclusion. Exclusion criteria were the presence of (i) intelligence quotient (IQ) lower than 70, (ii) 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 not to take benzodiazepines 12 hours prior to the neuropsychological assessment.

A total of 60 healthy controls (HC) without evidence of psychiatric or neurological history were recruited via advertisement. None of the controls had first-degree relatives with psychiatric

disorders. There were no differences between patients and healthy subjects in terms of age, gender, educational level and estimated IQ.

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice and approved by the Hospital Clinic Ethics and Research Board. All participants provided written informed consent prior to their inclusion in the study.

Assessment

Demographic, clinical, and psychosocial functioning measures

In order to gather main sociodemographic and clinical data, all patients were assessed by means of a semistructured interview based on the Structured Clinical Interview for DSM Disorders (SCID) (First, 1997), which also considered data from medical records. YMRS and HDRS-17 scores were also used to evaluate the severity of manic and depressive symptomatology, respectively.

Functional outcome was assessed by means 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.

Neuropsychological assessment

All participants completed a comprehensive neuropsychological battery in order to assess different cognitive domains including Processing Speed, Working Memory, Verbal Learning and Memory, Visual Memory, Executive Functions and Attention. This battery comprises the Digit-symbol Coding and the Symbol Search, Arithmetic, Digits, and Letter-Number sequencing subtests from Wechsler Adult Intelligence Scale (WAIS-III) (Wechsler, 1997), Phonemic (F-A-S) and Categorical (Animal naming) components of the Controlled Oral Word Association Test (COWAT) (Benton, 1976), Trail Making Test-A (TMT-A) and the Trail Making Test-B (TMT-B)

(Reitan, 1958), the California Verbal Learning Test (CVLT)(Delis et al., 1987), the Rey Osterrieth Complex Figure (ROCF) (Rey, 1997), the computerized version of the Wisconsin Card Sorting Test (WCST)(Heaton, 1981), the Stroop Colour-Word Interference Test (Golden, 1978), the Continuous Performance Test–II (CPT-II), version 5 (Conners, 2002). Finally, estimated IQ was assessed with the (WAIS-III) vocabulary subtest (Wechsler, 1997).

Social cognition assessment

In order to assess different SC domains, all participants were evaluated with the following tests:

(1) Theory of Mind (ToM) was assessed with two tests: (a) the Reading the Mind in the Eyes test (RMET) (Baron-Cohen et al., 2001) in which subjects are shown 36 photographs of a person's eyes and must select which of four words best describes what the person in the photograph is thinking or feeling. The RMET produces a single raw total score, with higher scores indicating better performance detecting mental states. (b) The Hinting Task (Corcoran et al., 1995) examines the ability of individuals to infer the true intent of indirect speech throughout 10 short passages reflecting an interaction between two characters. Higher scores indicate better performance. The present study used a reduced version with 5 stories of the Hinting Task, which has demonstrated good psychometric properties in the validated Spanish version (Gil et al., 2012).

(2) Emotional intelligence was evaluated using the Mayer–Salovey–Caruso Emotional Intelligence Test' (MSCEIT) (Mayer et al., 2003). This instrument consists of 141 items and provides eight task scores that measure the four branches of emotional intelligence: perceiving, using, understanding, and managing emotions. These branches can be assigned to the areas of emotional experience and emotional strategic. The test provides a total score and also scores in two areas, in the four branches and in each of the specific tasks that the test includes. Lower scores indicate poorer performance in emotional intelligence.

(3) Attributional bias was tested through the Ambiguous Intentions Hostility Questionnaire (Combs et al., 2007). It is focused on assessing the individual's tendency to over-attribute hostile intentions to others and to respond to others in a hostile manner. It is comprised of 15 situations that are ambiguous, intentional, and accidental in nature. The AIHQ produces bias scores in which higher scores reflect a more hostile, negative and personal attributional style, and more aggressive attributions.

Statistical analysis

All analyses were performed with SPSS version 23 (IBM Corp, Arkmonk, NY, USA). Initial analyses were conducted to compare demographic and clinical characteristics between patients with BD and HC using t-tests and $\chi 2$ tests (as appropriate).

Social Cognition and neuropsychological tests raw scores were standardized to z-scores (with a mean=0 and SD=1) based on HCs' performance. Outlying z-scores exceeding 4 SDs below HC's mean were truncated at z =-4.0. The z-scores for TMT-A, TMT-B, CPT-II and WCST perseverative errors were inverted so that lower scores were indicators of poorer performance. Six neurocognitive domains and ToM domain were calculated from mean z-scores compromising each domain: ToM (REMT total score and Hinting task, total score); (i) Processing Speed (WAIS-III Digit-symbol Coding subtest, Category fluency (Animal naming), and TMT-A); (ii) Working Memory (WAIS-III Letter-number sequencing and Digit-span); (iii) Verbal Memory (CVLT (total trials 1–5 list A, short free recall, short cued recall, delayed free recall, and delayed cued recall scores)); (iv) Visual Memory, (ROCF delayed recall)); (v) Executive Functions (WCST (number of categories and perseverative errors), Stroop Interference Test, and TMT-B); and (vi) Attention (CPT-II (omission, reaction time and reaction time standard error). Neurocognitive and ToM composites were standardized against the composite scores obtained by the HC group. Finally, an overall composite cognition z-score was established for each participant by averaging the six domains and standardizing this output based on the HCs' composite cognition score.

A hierarchical cluster analysis (HCA) was carried out in order to identify homogeneous subgroups of patients with BD based on their SC performance in terms of the different SC domain scores. Similarity between cases was computed with the Euclidian distance and Ward linkage was selected as the agglomeration procedure. Next, the dendrogram was visually inspected to establish the appropriate number of clusters to be retained. In addition, a discriminant function analysis (DFA) was also conducted in order to test the validity of the clusters. The SC profiles of the patients in the different clusters and the HC group were compared using a one-way ANOVA, with group membership (the two clusters and the HC group) as a fixed factor and the three SC domains as dependent variables. Tukey post-hoc comparisons were carried out to identify pair-wise differences between groups. Subsequently, comparisons (t-tests and χ^2, as appropriate) between the different clusters were carried out to examine possible differences in demographic, clinical, and neurocognitive variables. Finally, we conducted the logistic regression model with SC cluster groups as the dependent variable to estimate the effects of the risk factors associated with poor SC performance. The clinical, demographic and neuropsychological variables introduced in the logistic regression were based on the statistically significant results found in the univariate analysis. All analyses were two-tailed and significance was set at $p<0.05$.

RESULTS

Social Cognition's clusters

Results obtained from the HCA and data provided by visual inspection of the dendrogram indicated that 71 patients were optimally grouped, according to SC performance, into two different clusters: the first cluster representing the low performance group (LP) included 23 subjects (32.4%) while the second one corresponding to the adjusted performance group (AP), included 48 patients (67.6%).

The DFA revealed the presence of one discriminant function explaining 100% of the variance (Wilks' λ =0.291; χ2 =83.330; p <0.001). The emotional intelligence domain contributed most to classify bipolar patients into the different subgroups showing the highest standardized coefficient (0.929).

Comparison between patients with BD and HC

Table 1 shows baseline characteristics of the study sample. Comparisons between both groups revealed statistically significant differences in psychosocial functioning, the clinical group being the most functionally impaired (t=9.659; p≤0.001; BD>HC). Patients also showed higher subsyndromal depressive (t=5.732; p≤0.025; BD>HC) and manic symptoms (t=2.272; p≤ 0.001; BD>HC) (Table 1).

Comparison of SC between BD clusters and HC

The ANOVA analysis revealed a statistically significant main effect of group when comparing the two BD clusters and HCs (Table 2, Figure 1).

The first cluster had a low SC profile (LP group) with a statistical significantly poorer performance in all SC domains when compared to the AP group and HC groups. Specifically, patients in the LP group showed mild difficulties in ToM (z=-0.89; $F_{(2, 114)=}$11.90; p<0.001) and attributional bias (z=-0.69; $F_{(2, 110)=}$4.24; p=0.017) and moderate difficulties in emotional intelligence (z=-1.43; $F_{(2, 129)}$=35.50; p<0.001). Patients in the second cluster (AP group) performed comparably to HC on all SC domains (z-scores ranging from 0.08 to 0.36 above the HC's mean) with no significant differences between the two groups.

We also conducted comparisons between the two SC BD clusters and HC subjects across different SC tasks. The LP group performed significantly worse in most SC tasks than the AP group and HC. Patients in AP group outperformed HC in understanding emotion branch ($F_{(2, 129)}$=9.362; p=0.011; AP>HC) (see Supplementary Table S1).

Comparisons between the two SC profiles on demographic, clinical and neuropsychological variables

As reported in Table 3, concerning demographic variables differences between the two clusters were found with regard to gender (χ^2=5.578; p=0.018) and estimated IQ (t=2.599; p=0.011). Specifically, patients from the LP group were characterized by a lower percentage of females and showed a lower estimated IQ. Considering clinical variables, significant differences were observed among groups in subthreshold depressive symptomatology at the time of the assessment (HDRS t=-2.050; p=0.044) and illness duration (t=-2.127; p=0.037). Patients belonging to the LP group exhibited increased subthreshold depressive symptoms and longer illness duration compared to the AP group. Regarding neurocognitive performance, both groups significantly differed in terms of visual memory (t=2.400; p=0.019) and attention (t=2.501; p=0.015) (see Table 4). In all cases, patients from the LP group performed worse than patients in the AP group. No significant differences between clusters were found for the rest of cognitive domains.

Identifying factors associated with SC performance

A logistic regression analysis was performed to assess the role of the variables on the likelihood that patients belong to LP group. The variables included in the model comprised of those that were found to be significant when comparing both groups: estimated IQ, gender, illness duration, HDRS score, attention and visual memory performance. After running the logistic regression, it was found that the final model included only three significant variables explaining up 35.2% (Nagelkerke *R*-squared) of the variance of poor SC performance. The model correctly classified 70.8% of the cases. The variables contributing to the model were: low estimated IQ (β=-0.083; OR= 0.920; 95%CI=0.863-0.981; p=0.011), male gender (β=1.733; OR=5.661; 95%CI=1.473–21.762; p=0.012), and illness duration (β=0.082; OR=1.085; 95%CI=1.006–1.171; p=0.035). In comparison with the AP members, patients belonging to the LP group were more

likely to be male and to have a lower estimated IQ. In addition, the presence of longer illness duration increased the probability of low performance membership.

DISCUSSION

This is the first study aiming to identify profiles of patients based on their performance in different domains of SC by using a data-driven approach in a sample of euthymic patients with BD. Our results suggest the existence of two discrete patterns. First, our data reveal a cluster, labelled as the AP group, that constituted the 67.6% of the sample, characterized by patients with preserved social cognitive skills. Patients in the second cluster, the so-called LP group, was composed of 32.4% of the sample and showed mild difficulties in ToM and attributional bias domains and moderate impairment in emotional intelligence performance. The two distinct SC subgroups differed in terms of demographic, clinical and neurocognitive variables. Particularly, patients in the more affected group were more prone to be males, to present a lower estimated IQ, longer illness duration as well as more subsyndromal depressive symptoms. Concerning neurocognition, patients from this group showed lower performance outcomes in visual memory and attention domains when compared to patients with preserved SC. The logistic regression analysis showed that poorer SC was accounted for longer illness duration together with male gender and a lower estimated IQ.

Along with previous cognitive cluster analysis studies, our results demonstrated different SC severity performance among patients with BD. These differences ranged from intact SC performance to patients presenting mild/moderate impairment in SC domains (Burdick et al., 2014; Jensen et al., 2016; Jiménez et al., 2017; Lewandowski et al., 2014; Russo et al., 2017; Solé et al., 2016; Van Rheenen et al., 2017). However, while some studies found that 32%-48% of remitted patients are relatively cognitively intact (Burdick et al., 2014; Solé et al., 2016), our data revealed that around 68% of patients exhibited adjusted social cognitive abilities. This finding is consistent with several prior reports that indicate that SC would be relatively intact in a high

proportion of patients with BD (Burdick et al., 2014; Lee et al., 2015; Sperry et al., 2015; Van Rheenen & Rossell, 2014; Varo et al., 2017). It is worth highlighting that the current study focused exclusively on SC with different social cognitive domains by means of several tasks. In contrast, previous studies had included neurocognitive measures (Jensen et al., 2016; Lewandowski et al., 2014; Russo et al., 2017; Solé et al., 2016) and SC using solely one out of the four branches of the MSCEIT (Burdick et al., 2014; Jiménez et al., 2018; Van Rheenen et al., 2017) hence they did not sufficiently assess the dimensions of SC. We did not identify a subtype with global severe impairment across SC domains. The lack of this subgroup in our results suggests that more severe SC deficits might be associated with other conditions such as schizophrenia instead of BD (Derntl, Seidel, Schneider, & Habel, 2012; Lee et al., 2013). Our results would also be in line with previous studies, which support the presence of less severe impairment in SC compared to neurocognitive domains in patients with BD (Bilderbeck et al., 2016; Theory of mind and facial emotion recognition in euthymic bipolar I and bipolar II disorders, 2011; Pickup, 2008). This might suggest that improvement in SC might be not accompanied by changes in neurocognition (Green et al., 2019). This should be taken into account when interventions are designed and addressed. However, the nature of the relationship between neurocognition and SC is not yet completely understood (Ventura et al., 2013).

Our results were similar to those obtained in our previous study (Varo et al., 2017), in which euthymic patients were divided into three subgroups according to normative data and based on their performance in emotional intelligence through the complete MSCEIT. These findings contrast with the two SC clusters found in the current study. It is plausible that discrepancies in the number of emergent subgroups may be due to methodological differences between both studies. In the previous study, the cluster analysis was not used, and results were limited due to the absence of a control group and the lack of assessment of different SC domains such as ToM and the attributional bias. In contrast, the use of cluster analysis approach with different SC domains in the current study provides a further understanding of the specificity of social

cognitive deficits in BD through a deep characterization of SC clusters. Nevertheless, while previous studies revealed that patients had impairments of moderate magnitude in ToM and of small effect size in the emotional SC domain (Samamé, 2013), the results of the current study reveal that the emotional intelligence domain, unlike the other two SC domains, seems to play a key role in the differentiation between patients showing a preserved social cognitive performance and patients belonging to the lower social cognitive achievement group. It is also noteworthy that, as it has previously been suggested, emotional intelligence is particularly relevant in patients with BD since impaired mood regulation may be related to maladaptive patterns of information processing, specifically with emotional processing biases (Aparicio et al., 2017; Kjærstad et al., 2019; Varo et al., 2019). Literature on ToM and attributional bias domains show mixed findings. While some studies indicate that patients with BD might actually have these domains considerably preserved (Donohoe et al., 2012; Kerr et al., 2003), many others report deficits in patients with BD (Bora, Veznedaroğlu, & Vahip, 2016; Lahera et al., 2015; Samamé et al., 2015). Our findings are partially in line with the latter, that is, patients of the LP group showed mild/moderately impairment in ToM and attributional bias.

Further group comparisons provided information about the relationship between several demographic, clinical and neurocognitive factors and the specificity of SC profiles in BD. Patients from the LP group were characterized by a higher percentage of males, lower estimated IQ, presented longer illness duration and more subsyndromal depressive symptoms. These findings are in line with the results from other studies where several clinical and demographic variables such as male gender (Bücker et al., 2014; DeTore et al., 2018; Donges et al., 2012; Varo et al., 2019), low estimated IQ (Bilderbeck et al., 2016; Burdick et al., 2014; Varo et al., 2017), subthreshold symptoms (Lahera et al., 2015; Varo et al., 2017) and illness duration (Aparicio et al., 2017; Samamé et al., 2015) appear to increase the likelihood of significant SC impairment. However, other studies failed to find any association between SC and clinical variables (Bora et al., 2005; Martino, Strejilevich, Fassi, Marengo, & Igoa, 2011). Regarding neurocognitive

variables, patients from the LP group showed more cognitive deficits in visual memory and attention. However, when neurocognitive domains were entered in the logistic regression model these variables were no longer statistically significant. Therefore, as mentioned above and in agreement with previous studies (Bora et al., 2016; DeTore et al., 2018; Fanning, Bell, & Fiszdon, 2012; Hoe, Nakagami, Green, & Brekke, 2012) we found that neurocognitive ability may represent a 'necessary but not sufficient' prerequisite for social cognitive abilities.

In light of the above mentioned findings, and bearing in mind that longer illness duration and lower estimated IQ has been suggested to be associated with neurocognitive dysfunction (Bora, Yucel, & Pantelis, 2009; Burdick et al., 2014; Martínez-Arán et al., 2004; Vieta et al., 2018), one may argue that the aforementioned variables might also place a patient at increased risk for developing more generalized SC deficits. Although the temporal progression of SC dysfunction in BD is unclear, emerging evidences have found impairments in SC, in both patients with BD and their unaffected relatives, suggesting that deficits in SC may be considered a possible trait marker of genetic risk for BD (Bora & Özerdem, 2017; Kessing & Miskowiak, 2018; Kjærstad et al., 2019; Russo et al., 2017). Future prospective longitudinal studies ideally starting with high-risk population are therefore needed to elucidate the nature and developmental trajectory of SC deficits in BD.

The results have several implications for clinical and research perspectives. The differences in profiles revealed by this study imply that SC should be measured by several tasks corresponding to different dimensions to better define and pinpoint specific difficulties. This may have important implications for the non-pharmacological treatment of BD patients. Our findings highlight the need to characterize the pattern of impairment more accurately, to enable designing of programs specifically to tailored the SC dysfunction, while taking into consideration the needs of the impaired cluster. Thus, patients in the LP subgroup might optimally benefit from a specific type of targeted intervention focusing mainly on emotional intelligence, and then

on tasks related to ToM and attributional bias domains. Moreover, our findings shed more light on the hypothesis of specificity of social cognitive deficits in patients with BD, suggesting that difficulties in social cognitive abilities are characteristic of a subsample rather than being an overall deficit in BD. Taking into account that just one third of the sample of patients presented low SC performance, an assessment screening for SC would be useful before introducing a comprehensive assessment. This would also be necessary before initiating a treatment trial targeting SC to ensure inclusion of an enriched sample of patients with scope for improvement (Miskowiak et al., 2018). It may be possible to hypothesize that SC might act as a protective factor in the course of BD, given its role in facilitating adaptive social interactions, maintaining social relationships and in achieving social support (González-Ortega et al., 2019; Vlad et al., 2018). However, our study failed to detect any statistically significant relationship between SC and psychosocial outcomes in patients with BD. This was surprising given that one could assume that patients with BD who exhibit more persistent SC impairments would also experience greater functional difficulties in everyday life (Solé & Vieta, 2019). Nevertheless, it is important to mention that the association between both constructs is more complex since each of them encompasses multiple abilities and involves mediating variables (Green et al., 2019). Positive relationship between high IQ and better SC has been found (Bilderbeck et al., 2016; Van Rheenen et al., 2017; Varo et al., 2017), suggesting that IQ could be a good indicator of premorbid functioning, therefore, IQ may play a protective role against SC dysfunction among this group of patients (Jiménez et al., 2017).

The main strength of this study includes the clustering analysis using a comprehensive assessment of SC covering emotional intelligence, ToM and attributional bias. However, the study has some limitations that should be noted. First, our sample was recruited from a tertiary center, where some participants may represent a more severely affected subgroup of patients, which may affect the generalization of our results. Secondly, further studies with larger samples of patients with BD are needed in order to replicate our findings. Third, because of the cross-

sectional design, we were not able to determine the natural stability of these SC subtypes over the course of illness. Finally, we were unable to account for the effects of psychopharmacological treatments given because medication regimes vary widely and dosages were not controlled. Nevertheless, there were no differences concerning the type of psychopharmacological treatment among the two groups. Since at present there is not a validated screening to assess SC nor a validated comprehensive battery that covers different SC domains, this issue should be address in future research in BD.

In conclusion, our results suggest the existence of two discrete social cognitive profiles among euthymic patients with BD. Nearly two thirds of patients exhibited social cognitive abilities comparable to HC, suggesting that SC deficits in BD are not generalized but rather selective. Particularly male gender, together with a lower estimated IQ and longer illness duration may act as risk factors for low performance in SC in patients with BD.

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II. DISCLOSURES

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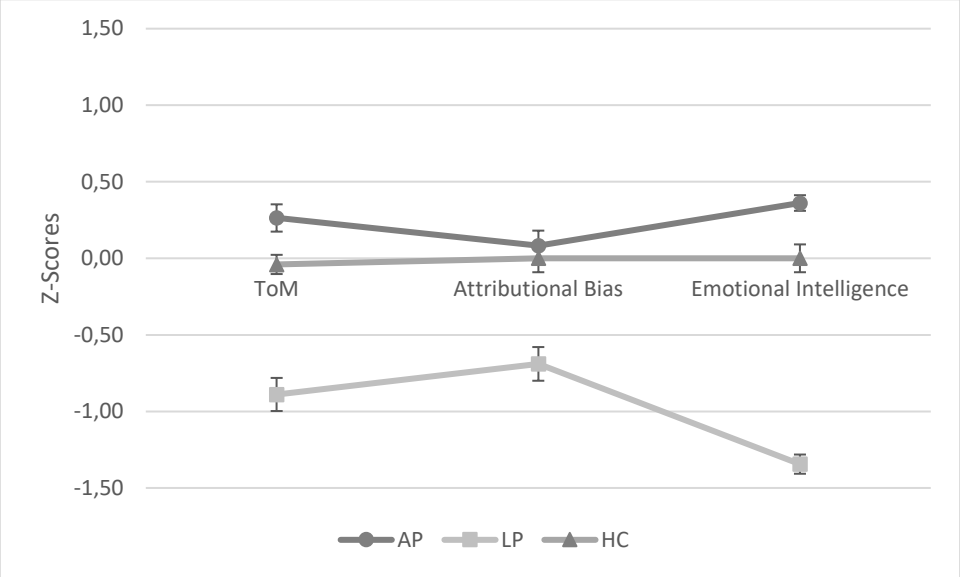
Figure(s) Click here to access/download;Figure(s);Figure 1.pdf

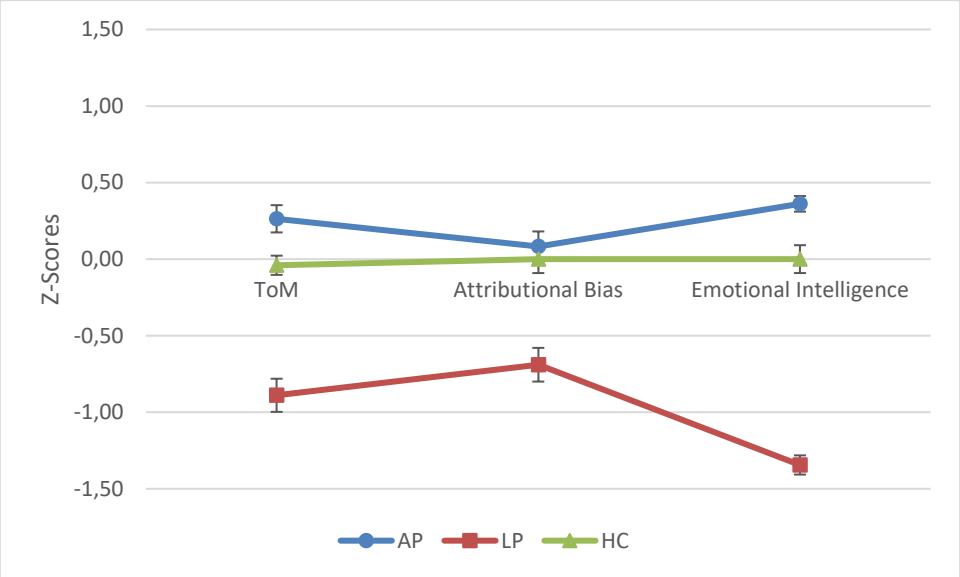
Figure 1. Comparison between the two social cognition bipolar disorder clusters and healthy subjects across social cognitive domains (Z scores)



ToM: Theory of Mind; LP: Low performance; AP: Adjusted performance; HC: Healthy Controls

Error bars depict standard error of the mean

Figure 1. Comparison between the two social cognition bipolar disorder clusters and healthy subjects across social cognitive domains (Z scores)



ToM: Theory of Mind; LP: Low performance; AP: Adjusted performance; HC: Healthy Controls

Error bars depict standard error of the mean

Table(1)

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Table 1. Comparison between euthymic bipolar disorder patients and healthy controls subjects in sociodemographic and clinical variables

	Bipolar patients (n=71) Mean (SD)	**Healthy controls (n=60)** Mean (SD)	**Statistical analyses**	
			t	**p**
Age	44.94 (9.35)	42.02 (10.54)	1.684	0.95
Educational level (years)	14.94 (3.01)	16.02 (4.74)	-1.515	0.418
Estimated IQ	107.77 (12.71)	109 (9.56)	-0.813	0.418
Age at onset	27.01 (9.06)			
Illness duration	17.86 (9.07)			
Total number of episodes	10.87 (11.80)			
Hypomanic episodes	3.17 (5.82)			
Manic episodes	2.42 (3.35)			
Depressive episodes	4.83 (6.112)			
Age at first hospitalization	32.02 (10.48)			
Number of hospitalizations	1.86 (2.04)			
HDRS	3.86 (2.19)	1.75 (1.94)	5.732	**<0.001**
YMRS	1.20 (1.26)	0.73 (1.06)	2.272	**0.025**
FAST Total score	19.77 (10.07)	5.92 (4.86)	9.659	**<0.001**
	N (%)	**N (%)**	**Chi Square**	**p**
Gender (female)	39 (54.9)	36 (60)	0.342	0.559
Diagnosis (BD-I)	53 (74.6)			
Lifetime psychotic symptoms (Yes)	42 (59.2)			
Psychotic symptoms in first episode (Yes)	23 (32.4)			
Axis I comorbidity (Yes)	14 (19.7)			
Axis II comorbidity (Yes)	16 (22.5)			

Axis III comorbidity (Yes)	32 (45.1)			
Family history of affective disorders (Yes)	48 (67.7)			
History of suicidal attempt	24 (33.8)			

Bold text in the table indicates significant values.

IQ: Intelligence Quotient; YMRS: Young Mania Rating Scale, HDRS: Hamilton Depression Scale, FAST: Functioning Assessment Short Test, BD-I: Bipolar disorder type I.

Table(2)
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Table 2. Comparison between the two social cognition bipolar disorder clusters and healthy controls across social cognitive domains (Z scores)

	LP N= 23 Mean (SD)	AP N=48 Mean (SD)	HC N=60 Mean (SD)			Post hoc tests		
				F	**p**	**LP vs. AP**	**LP vs. HC**	**AP vs. HC**
Theory of Mind	-0.89 (1.19)	0.26 (0.98)	-0.04 (0.69)	11.90	**<0.001**	**<0.001**	**0.002**	0.26
Attributional bias (AIHQ total)	-0.69 (1.21)	0.08 (1.08)	0.00 (1.00)	4.24	**0.017**	**0.016**	**0.044**	0.933
Emotional Intelligence (EIQ)	-1.34 (0.69)	0.36 (0.56)	0.00 (1.00)	35.50	**<0.001**	**<0.001**	**<0.001**	0.059

Bold text in the table indicates significant values.
LP: Low performance; AP: Adjusted performance; HC: Healthy Controls
EIQ: Emotional Intelligence quotient; AIHQ: Ambiguous Intentions Hostility Questionnaire

Table(3)

Click here to access/download;Table(s);table3_comparisons_groups_clinical

Table 3. Comparisons in sociodemographic and clinical between the two social cognitive clusters.

	LP n=23 Mean (SD)	AP n=48 Mean (SD)	**Statistical analyses**	
			t	**p**
Age	46.26 (8.72)	44.31 (9.67)	-0.819	0.415
Educational level (years)	14.78 (3.03)	15.06 (3.15)	0.355	0.724
Estimated IQ	102.35 (14.54)	110.43 (10.93)	2.599	**0.011**
Age at onset	24.61 (7.93)	28.17 (9.41)	1.565	0.122
Illness duration	21.09 (7.87)	16.31 (9.27)	-2.127	**0.037**
Total number of episodes	15.24 (17.52)	8.96 (7.65)	-2.083	0.128
Number of hypomanic episodes	4.43 (8.70)	2.63 (3.98)	-1.187	0.239
Number of manic episodes	3.64 (4.92)	1.94 (2.17)	-2.014	0.134
Number of depressive episodes	6.45 (8.68)	4.08 (4.40)	-1.521	0.133
Total number of episodes	15.24 (17.52)	8.96 (7.65)	-2.083	0.128
Number of hospitalizations	2.09 (2.43)	1.74 (1.85)	-0.655	0.515
Age at first hospitalization	32.76 (10.72)	30.29 (10.07)		
HDRS	4.61 (1.88)	3.49 (2.26)	-2.050	**0.044**
YMRS	1.09 (1.13)	1.26 (1.33)	0.523	0.603
FAST total	20.61 (10.61)	19.36 (9.89)	0.891	0.376
	N (%)	**N (%)**	**Chi Square**	**p**
Gender (male)	17 (23.9)	15 (21.1)	5.578	**0.018**
Employment status (not working)	12 (52.2)	23 (47.9)	0.113	0.737

Marital status (not married)	13 (56.5)	30 (62.5)	0.837	0658
Diagnosis (BD-I)	18 (78.3)	35 (72.9)	0.235	0.628
Axis I comorbidity (yes)	3 (14.3)	11 (22.9)	0.673	0.412
Axis II Comorbidity (yes)	5 (22.7)	11 (22.9)	0.001	0.986
Type first episode Mania Hypomania Depression	 9 (39.1) 3 (13) 11 (47.8)	 19 (39.6) 3 (6.3) 26 (54.2)	0.970	0.616
Predominant polarity Manic/hipomanic Depressive Unspecified	 5 (23.8) 4 (19) 12 (57.1)	 11 (22.9) 9 (18.8) 28 (58.3)	0.009	0.995
Lifetime psychotic symptoms (Yes)	12 (52.5)	30 (62.5)	0.686	0.407
Family history affect. disorders (Yes)	6 (72.7)	32 (69.6)	0.072	0.789
Family history psychiatric. disorders (Yes)	18 (81.8)	39 (81.3)	0.003	0.955
History of suicidal attempt	3 (13.6)	7 (14.9)	2.171	0.338
Current medications				
Mood stabilizers (yes)	23 (100)	43 (89.6)	2.577	0.108
Antipsychotic (yes)	16 (69.6)	32 (66.7)	0.060	0.807
Antidepressant (yes)	14 (60.9)	30 (62.5)	0.18	0.895

Anxiolytic (yes)	7 (30.4)	11 (23.4)	0.400	0.527

Bold text in the table indicates significant values.

LP: Low performance; AP: Adjusted performance, IQ: Intelligence Quotient, HDRS: Hamilton Depression Rating Scale, YMRS: Young Mania Rating Scale, BD: Bipolar disorder; FAST: Functioning Assessment Short Test

Table(4)

Click here to access/download;Table(s);table4_comparisons_groups_cogniti

Table 4. Comparisons in neurocognitive domains between the two social cognitive clusters.

	LP Mean (SD)	AP Mean (SD)	**Statistical analyses**	
			t	**p**
Processing speed	-1.22 (1.52)	-1.35 (0.82)	-0.492	0.624
Verbal learning and memory	-0.41(1.09)	-0.169 (1.00)	0.902	0.370
Working memory	0.09 (0.45)	0.05 (0.45)	-0.450	0.654
Visual memory	-0.63 (1.12)	-0.03 (0.91)	2.400	**0.019**
Executive functions	-0.34 (0.99)	-0.04 (0.74)	1.408	0.164
Attention	-1.36 (1.67)	-0.49 (1.14)	2.501	**0.015**
NCI	-0.99 (1.13)	-0.92 (1.38)	0.213	0.83

Bold text in the table indicates significant values.

LP: Low performance; AP: Adjusted performance; Neurocognitive Composite Index

Other Supplementary Material
Click here to access/download;Other Supplementary Material;Table S1.docx

Table S1. Comparison between the two social cognition bipolar disorder clusters and HC subjects across social cognitive domains and tasks (Z scores)

	LP	**NP**	**HC**					
	N= 23	**N=48**	**N=60**					
	Mean (SD)	Mean (SD)	Mean (SD)	**F**	**p**	Post hoc tests		
						LP vs. AP	**LP vs. HC**	**AP vs. HC**
Theory of Mind	-0.89 (1.19)	0.26 (0.98)	-0.04 (0.69)	11.90	**<0.001**	**<0.001**	**0.002**	0.26
RMET	-0.74 (1.21)	0.17 (0.95)	0.00 (1.00)	6.450	**0.002**	**0.002**	**0.012**	0.684
Hinting Task	-0.58 (0.98)	0.11 (0.91)	0.00 (1.00)	4.259	**0.016**	**0.014**	**0.048**	0.851
Emotional Intelligence (EIQ)	-1.34 (0.69)	0.36 (0.56)	0.00 (1.00)	35.50	**<0.001**	**<0.001**	**<0.001**	0.059
Areas								
Experiential area	-1.34 (0.69)	0.36 (0.56)	0.00 (1.00)	9,696	**<0.001**	**<0.001**	**0.001**	0.698
Strategic area	-0.98 (0.86)	0.39(0.88)	0.00 (1.00)	16.841	**<0.001**	**<0.001**	**<0.001**	0.081
Branches								
Perceiving emotions	-1.22 (0.77)	0.25 (0.85)	0.00 (1.00)	21.373	**<0.001**	**<0.001**	**<0.001**	0.340
Using emotions	-0.98 (0.79)	0.19 (0.77)	0.00 (1.00)	14.220	**<0.001**	**<0.001**	**<0.001**	0.524
Understanding emotion	-0.48 (1.22)	0.57 (0.88)	0.00 (1.00)	9.362	**<0.001**	**<0.001**	0.131	**0.011**
Managing emotions	-1.08 (0.84)	0.15 (0.98)	0.00 (1.00)	13.69	**<0.001**	**<0.001**	**<0.001**	0.710
Attributional bias (AIHQ total)	-0.69 (1.21)	0.08 (1.08)	0.00 (1.00)	4.24	**0.017**	**0.016**	**0.044**	0.933
AIHQ-HB Hostility	-0.25 (1.83)	0.05 (1.37)	0.00 (1.00)	0.596	0.553			
AIHQ-IS Intentionality	0.59 (1.39)	0.09 (1.01)	0.13 (1.29)	3.131	**0.048**	0.069	0.058	0.986
AIHQ-BS Blame	-0.45 (1.25)	0.11 (1.14)	0.12 (1.24)	2.047	0.134			
AIHQ-AS Angry	-0.83 (1.50)	-0.08 1.34)	0.13 (1.30)	3.827	**0.025**	0.078	**0.021**	0.755
AIHQ-AB Aggressivity	-0.47 (1.35)	0.14 (0.81)	0.12 (1.23)	2.682	0.073			

Bold text in the table indicates significant values.
LP: Low performance; AP: Adjusted performance; HC: Healthy Controls
EIQ: Emotional Intelligence quotient; AIHQ: Ambiguous Intentions Hostility Questionnaire

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April 30th, 2020

Editor-in-Chief
Psychological Medicine
Dr. Kenneth S. Kendler and Dr. Robin M. Murray

Ref.: Ms. No. PSM-D-19-01692
IDENTIFYING SOCIAL COGNITION SUBGROUPS IN EUTHYMIC PATIENTS WITH BIPOLAR DISORDER: A CLUSTER ANALYTICAL APPROACH
Dr. Kenneth S. Kendler and Dr. Robin M. Murray,

Thank you for giving us the opportunity to resubmit our manuscript. We feel that the present version has largely benefited from the comments of the reviewers and we wish to express our gratitude to them.
In the manuscript showing our revisions, you will find newly inserted text marked with yellow, and deleted text marked with ~~red~~. Please read below a comprehensive and detailed list of changes and answers made in response to the questions raised by the reviewer.

We really hope that you will find the new version suitable for publication. What follows is a point-by-point response to reviewers' comments.

Reviewer #1:

Reviewer's comment*: Social cognition and its different components are poorely defined.*

Reply: We agree that social cognition and its different components should be explained more clearly. Accordingly, we have made the following addition to the introduction of the manuscript:

Introduction, p.: 3

SC is a multifaceted construct that encompasses a complex set of mental processes including perceiving, interpreting, and generating responses to the intentions, dispositions, and behaviors of others that underlies social interactions and that enable successful and adaptive behavior in a social context (Harvey & Penn, 2010). It involves four core domains including the Emotional Intelligence, Theory of Mind (ToM), Attributional Bias, Social Perception and Knowledge. Specifically, ToM is the ability to comprehend and represent mental states of others, including the inference of intentions, dispositions, and/or beliefs. Next, the ability to share experiences and emotions of others, as well as the capacity to regulate one's emotional responses to others is known as Emotional Intelligence (EI). The Attributional Bias (AB) refers to the way in which individuals explain or reason of the causes of social events or interactions. Finally, the ability to decode and interpret social cues in others is called Social Perception and Knowledge (Green et al., 2008; Sergi et al., 2007).

Reviewer's comment: *I believe that a more thorough discussion about the implications of the reported findings should be included and statements that are not supported by the findings of the study should be avoided (For instance, the authors state that "patients with unimpaired SC showed fewer subsyndromic depressive symptoms, shorter illness duration and higher IQ, suggesting that a successful SC might contribute to resilience").*

Reply: We agree with the reviewer that further discussion about the implications or interpretation of the reported finding would be beneficial to the manuscript. We have therefore added the following contents regarding clinical implications to the manuscript:

Discussion, p. 13: Our results would also be in line with previous studies, which support the presence of less severe impairment in SC compared to neurocognitive domains in patients with BD (Bilderbeck et al., 2016; Igoa et al., 2011; Pickup, 2008). This might suggest that improvement in SC might be not accompanied by changes in neurocognition (Green et al., 2019). This should be taken into account when interventions are designed and addressed. However, the nature of the relationship between neurocognition and SC is not yet completely understood (Ventura, Wood, & Hellemann, 2013).

Discussion, pp 13-14: Our results were similar to those obtained in our previous study (Varo et al., 2017), in which euthymic patients were divided into three subgroups (…). These findings contrast with the two SC clusters found in the current study. It is plausible that discrepancies in the number of emergent

subgroups may be due to methodological differences between both studies. In the previous study, cluster analysis was not used, and results were limited due to the absence of a control group and the lack of assessment of different SC domains such as ToM and the attributional bias. In contrast, the use of cluster analysis approach with different SC domains in the current study provides a further understanding of the specificity of social cognitive deficits in BD through a deep characterization of SC clusters.

Discussion, p. 16: The results have several implications for clinical and research perspectives. The differences in profiles revealed by this study imply that SC should be measured by several tasks corresponding to different dimensions to better define and pinpoint specific difficulties. This may have important implications for the non-pharmacological treatment of BD patients. Our findings highlight the need to characterize the pattern of impairment more accurately, to enable designing of programs specifically to tailored the SC dysfunction, while taking into consideration the needs of the impaired cluster. Thus, patients in the LP subgroup might optimally benefit from a specific type of targeted intervention focusing mainly on emotional intelligence, and then on tasks related to ToM and attributional bias domains.

Also, in accordance with the reviewer's comment we deleted in the text the following statement "*patients with unimpaired SC showed fewer subsyndromic depressive symptoms, shorter illness duration and higher IQ, suggesting that a successful SC might contribute to resilience*"). We have also omitted in thetext the statement concerning to the concept of resilience since it was a hypothetic argument and not totally supported by the finding of the study.

Discussion, p. 17: ~~Another important issue is that patients with unimpaired SC showed fewer subsyndromic depressive symptoms, shorter illness duration and higher IQ, suggesting that a successful SC might contribute to resilience. This construct makes reference to the process of adapting well in face on adversity or significant sources of stress, such as family and relationship problems, for instance. Being resilient doesn't mean that a person doesn't experience difficulties or distress. Probably, some factors as resilience or cognitive reserve may explain a significant amount of variance in functional outcome~~

Reviewer's comment *I believe that the word "decline" should be replaced by "abnormalities", "deficits" or "dysfunction" as there is no consistent evidence for donnward sloping of cognitive funcioning in BD.*

Reply: Thank you for this comment. In keeping with the reviewer's suggestion, we have replaced the word 'decline' by '*dysfunction*'.

Discussion, p. 15: In light of the above, and bearing in mind that longer illness duration and lower estimated IQ has been suggested to be associated with neurocognitive ~~decline~~ dysfunction**.**

Discussion, p. 16: (…) IQ could be a good indicator of premorbid functioning, therefore, IQ may play a protective role against SC ~~decline~~ dysfunction among this group of patients.

Reviewer's comment *Language revision is needed*

Reply: We thank the reviewer for bringing this to our attention. The manuscript has been revised by a native speaker in order to improve the final version.

Reviewer #2: *This original article from Varo and colleagues, "Identifying social cognition subgroups in euthymic patients with bipolar disorder: a cluster analytical approach" is an analytical study which compared BP patients to healthy controls (HC) with psychometric measurement on cognition. The overall article is well written and organized into different parts.*

Introduction part enlightens the importance of social cognition in BP patients and the lack of strong data described in the literature. The aim of this article was to explore social cognition (SC) profiles in euthymic BP patients, comparatively to controls. The authors also wanted to examine SC profiles regarding to demographic, clinical and neuropsychological variables.

Methods part mention a good description of the sample selection, assessment and statistical analysis.

In the Result part, description of SC clusters (Low performance group: LP ; and Adjusted performance group: AP), comparison between BD and HC, comparison between SC profiles on demographic, clinical and neuropsychological variables, and factors associated with SC performance has been done.

Discussion part compared findings with previous data of the literature which is well reviewed and stressed implications for clinical and future research. There is a good description of the limitations of the study.

The overall article is original and will be of great interest for the readers of Psychological Medicine.

Reply: Authors are grateful to the reviewer for his/her positive and encouraging comments.

We really hope that all the above described changes will fulfil your expectations and turn the paper into suitable for publication in your prestigious journal. We thank the reviewers for the suggestions that have contributed to improving the final version.

Yours sincerely,

Eduard Vieta