DURATION OF UNTREATED ILLNESS AND DEPRESSION SEVERITY ARE ASSOCIATED WITH COGNITIVE IMPAIRMENT IN MOOD DISORDERS

Running head: Cognition and DUI in mood disorders

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Abstract

Introduction: In this study we estimated the rate and the trajectory of cognitive impairment in a naturalistic sample of outpatients with major depressive disorder (MDD) and bipolar disorder (BD) and its correlation with different variables.

Materials and methods: An overall sample of 109 outpatients with MDD or BD was assessed for multiple clinical variables, including duration of untreated illness (DUI), and tested using the Montreal Cognitive Assessment (MoCA) during Major Depressive Episodes (MDE) and after remission. Correlations between MoCA scores and the clinical variables were then computed.

Results: About 50% of patients with MDD and BD showed mild cognitive impairment during MDE. Improvement of cognitive function between depression and remission was significant, even though residual symptoms were observed especially in the most impaired patients. Of note, cognitive performance during depression was negatively associated with depression severity and DUI.

Discussion: Present findings confirm available evidence about patterns of cognitive impairment in mood disorders, in terms of prevalence and persistence beyond remission in most severe cases. Moreover, a longer DUI was associated with worse cognitive performance during depression, and consequently with poorer outcome, underlining the importance of prompt treatment of these disorders also in light of a cognitive perspective.

Keywords: bipolar disorder, cognitive dysfunction, duration of untreated illness, major depressive disorder, Montreal cognitive assessment

Introduction

Over the last decades, the number of scientific publications addressing neurocognitive impairment in mood disorders has been constantly growing(Russo, Mahon, & Burdick, 2015). It is now well established that cognitive impairment is one of the core features of mood disorders, emerging during depressive episodes in major depressive disorder (MDD) and during depressive and manic phases in bipolar disorder (BD). Moreover, there is evidence for the persistence of cognitive impairment beyond mood episodes during euthymia(Dell'Osso et al., 2015). A number of clinical characteristics has been associated with cognitive impairment in mood disorders and the severity of the impairment has been related to several clinical factors(McIntyre et al., 2013). First of all, age is an important moderator of cognitive performance with an inversely proportional relationship between age and cognitive performance(Lee, Hermens, Porter, & Redoblado-Hodge, 2012). Moreover, cognition of depressed patients is thought to be influenced by childhood traumatic events(Lemos-Miller & Kearney, 2006; Riso, Miyatake, & Thase, 2002), education level(Gildengers et al., 2012), age at onset(Herrmann, Le Masurier, & Ebmeier, 2008), duration of illness(Herrera-Guzman et al., 2010), frequency of depressive episodes(Gorwood, Corruble, Falissard, & Goodwin, 2008) and by psychiatric(Liu, Chiu, & Yang, 2010) and medical comorbidities(McIntyre et al., 2007)[20,2]. Another significant factor is the effect of psychotropic drugs(McIntyre et al., 2013): for instance, antidepressants have been associated with memory and verbal learning deficits, but with better cognitive flexibility(Lee et al., 2012). Indeed, evidence on the real effect of antidepressants on cognition is still inconclusive. It is also known that antipsychotics have been correlated with deficits in working memory(Baune & Renger, 2014). Cognitive impairment

characterizes both MDD and BD: few studies, however, have directly compared the cognitive profile of patients with MDD and BD during depressive episodes. In addition, these studies included patients regardless of the disease phase and produced conflicting evidence, suggesting in some cases a different profile of dysfunctions in unipolar versus bipolar patients (in terms of expression and severity), as well as overlapping deficits in other reports(Xu et al., 2012).

Evidence in this field has been summarized in a recent metanalysis of the comparative studies of cognitive functioning in BD and MDD, performed by Samamè and colleagues (Samamé, Szmulewicz, Valerio, Martino, & Strejilevich, 2017), revealing that there might be no distinctive feature between BD and MDD patients in terms of neuropsychological profile. In fact, Authors found similar neuropsychological outcomes in the two disorders across eleven cognitive domains during depression. However, a significant heterogeneity in effect sizes was observed and studies included in the analyses had very limited sample sizes.

Studies published after the metanalysis by Samamè and co-authors have still produced conflicting evidence. Specifically, in a recent study comparing the cognitive function of patients with MDD, BD, relatives of BD and MDD patients and healthy controls, Bo and colleagues did not find specific differences between unipolar and bipolar patients, but only differences in the degree of dysfunction (Bo et al., 2018). In contrast with these results, Mak and co-authors (Mak et al., 2018) found evidence of greater cognitive impairment in unipolar compared to bipolar depression, with regard to executive functions and psychomotor speed in drug-naive patients.

Follow-up studies of longitudinal course of cognitive impairment are essential but difficult to carry out. With regard to BD, t~~T~~he few existing ones suggest that executive

functions and processing speed are the two domains stably altered over time in bipolar patients, regardless of change in psychiatric symptom severity~~cognitive impairment is stable over time in BD~~(Balanza-Martinez et al., 2005; Depp et al., 2008; Mur, Portella, Martinez-Aran, Pifarre, & Vieta, 2008). With regard to MDD, most comprehensive data from a recent meta-analysis suggest that memory and attention deficits persist in remission from a major depressive episode (Semkovska et al., 2019): nonetheless, the analyses in this study were conducted on remitted patients instead of a longitudinal assessment of patients from depression to remission.

In this scenery, literature is inconclusive and it is still debated whether cognitive impairment is associated with distinct clinical features in MDD and BD patients, and if the two subtypes of mood disorders are characterized by different rates of cognitive impairment in clinical settings.

In this study, we used data from routine psychopathological and cognitive screening in order to estimate the rate, the nature and the longitudinal course of cognitive impairment in a naturalistic cohort of outpatients suffering from unipolar and bipolar depression. Moreover, we assessed the correlation of cognitive impairment in depressed and remitted patient with a range of socio-demographic and clinical characteristics, particularly age, age at onset, severity of depression and anxiety symptomatology, duration of illness and duration of untreated illness (DUI). A specific hypothesis we wanted to test regarded the relationship between DUI and cognitive impairment, considering the significant role DUI has demonstrated on outcome in several psychiatric disorders(Altamura, Dell'Osso, Mundo, & Dell'Osso, 2007). To the best of our knowledge, to date evidence regarding a specific association between DUI and cognitive impairment in mood disorders is still lacking.

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A secondary endpoint was to highlight differences between the cognitive profile of unipolar and bipolar during and after a MDE.

Materials and methods

Eligibility for the study

The present prospective, observational and naturalistic study was conducted at the Centre for the Diagnosis and Treatment of Depressive Disorders (CTDD) of ASST Fatebenefratelli-Sacco in Milan: an outpatient, tertiary psychiatric service dedicated to the treatment of patients with mood and anxiety disorders. In the study, both outpatients and patients undergoing day-hospital care were enrolled.

Although conceived before its publication, we underline the design of the study fits most of the methodological criteria defined by the International Society for Bipolar Disorders (ISBD) task force in the guidelines for the study of cognitive disorders in Bipolar Disorder (Miskowiak et al., 2017), as well as those previously proposed by Burdick and colleagues (2015)(Burdick, Ketter, Goldberg, & Calabrese, 2015).

Subjects of male and female gender, above the age of 18, satisfying the diagnosis of MDE (single or recurrent) within MDD or BD-I or BD-II were considered eligible for the study. Diagnoses were formulated through a structured clinical interview complying with the criteria of the Diagnostic and Statistical Manual of Mental Disorders - Fifth Edition (DSM-5). Exclusion criteria are reported in Table 1. Bipolar patients during a Mixed Episode as well as bipolar patients with subthreshold manic symptoms were excluded from the analyses.

Through a retrospective chart review, both in paper and computerized form or, when necessary, through a direct interview with the subject enrolled in the study, the main

socio-demographic and clinical characteristics of the patients were collected in an electronic database (see Table 2). In particular, data on DUI were collected: as in previuos studies by our research group(Altamura, Dell'osso, D'Urso, et al., 2008; Altamura, Dell'osso, Vismara, & Mundo, 2008; Dell'Osso et al., 2016; Galimberti et al., 2019), defining it as the time elapsed between the psychiatric onset and the first adequate treatment for MDD or BD, that is an antidepressant in the first case, mono-therapy with mood stabilizers or SGAs (or the combination of antidepressants with mood stabilizers or FGA/SGAs) in the latter case (Fountoulakis et al., 2017; Yatham et al., 2018). DUI was assessed during clinical interviews and cross-checked with data derived from paper medical records and/or Institutional electronic databases. When data about DUI weren't collectable as well as in case of low reliability of data (by researchers' judgement), patients were excluded from the analyses.

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All subjects enrolled in the study provided informed consent to the collection of personal and sensitive data, as well as the consent to undergo the psychometric evaluation and cognitive test described below.

Psychopathological assessment

The severity of depressive symptomatology was assessed by administering the 21 items-Hamilton Depression Rating Scale (HDRS)(Hamilton, 1960) at the time of study entry (depressive phase) and subsequently, repeatedly, until clinical remission (remission) was achieved (according to literature, remission was defined as a HDRS total score of less than 8). At the time of study entry (depression) and at remission (remission), the severity of the anxious component was also assessed by administering the Hamilton

Anxiety Rating Scale (HARS)(Hamilton, 2018). Clinical remission was considered complete upon the achievement of a concomitant score of HDRS<8 and HARS<7. HDRS and HARS were considered for the analyses of our study, but they were part of a more comprehensive psychopathological assessment including the Young Mania Rating Scale (YMRS)(Young, Biggs, Ziegler, & Meyer, 1978) we use to exclude bipolar patients with concomitant manic symptoms.

Cognitive screening: the Montreal Cognitive Assessment (MoCA)

In this study, cognitive performance was assessed through the Montreal Cognitive Assessment (MoCA), administered during the depressive episode and after clinical remission.

The MoCA is a short screening test developed by Nasreddine and colleagues (2005) for the identification of mild cognitive impairment (or MCI)(Nasreddine et al., 2005). The MoCA examines six different cognitive domains, such as: executive functions, visuospatial abilities, attention, verbal fluency, memory and spatio-temporal orientation. The total score of the MoCA ranges from a minimum of 0 to a maximum of 30, providing a global assessment of the cognitive performance of the subject. In relation to the years of education, a score equal to or above 26 is considered normal(Nasreddine et al., 2005), and a supplementary point is added if years of education are less than 12. The average time to administer the test is usually around 10-15 minutes.

The MoCA has good internal consistency with a Cronbach's alpha value of 0.83(Nasreddine et al., 2005). Furthermore, the sensitivity and the specificity of the MoCA in identifying MCI were 90% and 87%, respectively. Finally, the positive (VPP) and negative (VPN) predictive value of the MoCA were 89% and 91% for MCI.

Among cognitive screening tests, the Mini Mental State Examination (MMSE)(Folstein, Folstein, & McHugh, 1975) is the most commonly used for the detection of cognitive impairment. However, the MMSE is considered less sensitive in detecting deficits in executive functions, attention and visuospatial domains(Mitchell, 2009; Nasreddine et al., 2005). Compared to the MMSE, the MoCA includes several tasks based on visuospatial material and procedures specifically aimed at evaluating executive functions and attention(Smith, Gildeh, & Holmes, 2007), as well as memory.

The MoCA has proven to be a sensitive tool for screening patients with other forms of dementia, such as vascular dementia(Freitas, Simoes, Alves, Vicente, & Santana, 2012), dementia associated with Parkinson's disease(Hoops et al., 2009) and Frontotemporal Dementia(Freitas, Simoes, Alves, Duro, & Santana, 2012). In psychiatric practice, the MoCA has been used successfully to evaluate cognitive impairment in patients with depression, BD and schizophrenia(Musso, Cohen, Auster, & McGovern, 2014; Yang et al., 2018) as well as depressed patients undergoing electroconvulsive therapy (ECT)(Moirand et al., 2018). For these reasons, the MoCA was implemented in our daily clinical practice as a systematic cognitive screening tool.

Statistical analysis

The Kolmogorov-Smirnov and Shapiro-Wilk tests were performed to test the assumption of normal distribution of clinical and socio-demographic variables, as well as that of HDRS, HARS and MoCA scores.

Socio-demographic and clinical characteristics were compared between MDD and BD patients ~~the two groups~~ using Mann-Whitney *U* non-parametric test for continuous variables and Chi-square test ($\chi 2$) for dichotomous variables.

Then, Mann-Whitney *U* test was used to analyse the differences between the scores of the single cognitive domains of the MoCA between the two groups and between the total scores of the scales for depression and anxiety. ~~These analyses were conducted for both the depressive and remission-related scores~~

The mentioned analyses were conducted separately for data collected at each time-point (during depression and after clinical remission).

Furthermore, the statistical significance of the change of the MoCA total scores and of the individual cognitive domains from depressive phase to clinical remission was calculated using the Wilcoxon test.

The same analyses were also performed comparing two groups of patients defined by the presence of a MoCA score in the depressive phase below 26/30: "bipolar patients with cognitive dysfunction" and "unipolar patients with cognitive dysfunction".

In addition, the associations between MoCA score during depression and a series of socio-demographic and clinical variables were investigated, both for the group of patients with MDD and for the group with BD. Given the non-normal distribution of the values of the main variables, the strength of the association was calculated by means of the Spearman's rho (ρ) correlation coefficients.

For all analyses, the threshold for statistical significance was set at $p<0.05$.All statistical analyses were performed using IBM Statistical Package for Social Sciences version 22.0.

Results

Sample characteristics

In total, 109 outpatients with MDE were eligible for the study, including 72 patients (66.1%) diagnosed with MDD and 37 patients (33.9%) with BD. The two groups of patients with MDD and BD were homogeneous with regard to most of the main socio-demographic and clinical variables (see tables 2 and 3).

A statistically significant difference emerged in terms of previous hospitalizations (χ^2=14.924, p<0.001) and previous suicide attempts (χ^2=4.688, p=0.030), which were higher in the group of BD patients, who also had more mood episodes compared to patients with MDD (U=566.0, Z =-4.028, p<0.001).

~~Finally, in terms of medication status, patients with BD were more frequently treated with antipsychotics (χ^2=5.541, p=0.019) and mood stabilizers (χ^2=23.096, p<0.001), but less frequently with antidepressants (χ^2=8.224, p=0.004) compared to patients with MDD. However, there was no difference in treatment with benzodiazepines (χ^2=1.097, p=0.295). In our opinion, these differences reflect the naturalistic context in which the study was conducted. In fact, in clinical practice, MDD and BD are distinct by a different course of illness and by treatment strategies. We took into consideration these differences by conducting some analyses to weight their impact on the variables examined in the present study.~~

During depression, mean HDRS score and mean HARS were respectively 27.35±6.05 and 21.61±9.062 for MDD, and 26.62±6.45 and 18.68±7.32 for BD patients. Therefore, the study sample showed moderate to severe depressive symptomatology and mild to moderate anxious symptomatology, reflecting recruitment in a day-hospital service that is specifically dedicated to the treatment of severe forms of depression. No statistically significant differences emerged between the two groups with respect to depressive

(U=1265.5, Z=-0.311, p=0.756) nor to anxious symptomatology (U=1054.5, Z=-1.557, p=0.115).

Mean duration of current MDE (or time to remission) was 79.77 days in the total sample, with no statistical significant difference between MDD and BD (MDD: 77.43±34.85 vs BD: 84.32±37.84; U=1195.5, Z=-.875, p=.382).

Effect of pharmacological treatments on cognitive performance

With regard to medication status, our data show that patients with BD were more frequently treated with antipsychotics (χ^2=5.541, p=0.019) and mood stabilizers (χ^2=23.096, p<0.001), but less frequently with antidepressants (χ^2=8.224, p=0.004) compared to patients with MDD. However, there was no difference in treatment with benzodiazepines (χ^2=1.097, p=0.295). In our opinion, these differences reflect the naturalistic context in which the study was conducted. In fact, in clinical practice, MDD and BD are distinct by a different course of illness and by treatment strategies. We took into consideration these differences by conducting some analyses to weight their impact on the variables examined in the present study.

As described, the present study was conducted in a naturalistic context: coherently, the two groups of patients with MDD and with BD showed statistically significant differences in terms of pharmacological treatment. In fact, according to international guidelines, treatment of bipolar depression differs from that of unipolar depression. In particular, use of antidepressants in bipolar depression is controversial and should be considered second choice or, at least, it should be administered in association with a mood-stabilizer(Pacchiarotti et al., 2013). For this reason, depressed patients were more frequently on antidepressants in our sample, whereas bipolar patients were more often

on antipsychotic and mood stabilizing treatment. More detailed analyses were therefore conducted to investigate the effect of these different treatment patterns on the cognitive performance in our sample. To do so, we divided the total sample by comparing MoCA scores between patients according to their medication status. No statistically significant differences emerged between the MoCA total scores of subjects treated with versus without antidepressants (U=489.5, Z=-0.343, p=0.731). There were no differences even for antipsychotics (U=1230, Z=-1.135, p=0.257), mood stabilizers (U=748.5, Z=-0.509, p=0.611) and benzodiazepines (U=1212.5, Z=-0.571, p=0.568). Moreover, patients with different types of treatment were homogeneous even when considering the single domains of the MoCA and even after the analysis was conducted considering MDD and BD separately.

Cognitive performance during depression

The mean MoCA total score (adjusted for education level) in the entire sample of depressed patients enrolled in the study was 24.04± 3.94, lower than the normality cut-off of 26, as defined by the normative studies of the test. Globally, 50.5% of the subjects enrolled for the study had mild cognitive impairment, defined as a MoCA score of less than 26. In the two groups, 54.2% of patients with MDD and 59.4% of patients with BD had cognitive impairment, with a mean MoCA score of 24.11±4.04 and 23.89±3.78 respectively, and no statistically significant difference (U=1274.0, Z=-0.373, p=0.709).

In literature, there are no defined cut-offs for each single domain of the MoCA, however, it was possible to consider scores based on their maximum value. The Memory domain score varies from 0 to 5; the domains of Visuospatial Skills and of the

Executive Functions from 0 to 4; the domains of Attention, Language and Orientation score from 0 to 6. All MoCA single domains scores are reported in Table 4.

As mentioned, 54.2% of patients with MDD and 59.5% of patients with BD presented a picture of cognitive dysfunction during depression. Taking into consideration only these patients (with a MoCA total score below 26), the mean MoCA score was 21.18±3.16 for "MDD with cognitive dysfunction" and 21.59±3.11 for "BD with cognitive dysfunction", with no statistically significant differences (U=379.5, Z=-0.751, p=0.453). Moreover, the two groups were homogeneous in terms of severity of depressive and anxious symptomatology, with a mean HDRS score of 24.79±6.42 and 26.68±4.89, respectively in patients with MDD and with BD (U=341.5, Z=-1.317, p=0.188), and a HARS score of 20.42±8.92 and 18.73±7.56, respectively (U=373.0, Z=-0.691, p=0.489).

After analysing the six domains of the MoCA in the two subgroups, no statistically significant differences between MDD and BD were observed.

Patients with "MDD with cognitive dysfunction" were on average older than patients with "MDD without cognitive dysfunction" (61.59 vs. 49.91, p=0.001), had higher age of onset (38.64 vs. 28.55, p=0.004) and longer duration of untreated illness (62.41±65.83 months vs. 56.73±105.0 months; U=434.5, Z=-2.393, p=0.017). On the other hand, no statistically significant difference emerged in terms of number of mood episodes (p=0.489) and severity of depressive symptoms (p=0.484) and anxiety (p=0.188).

Conversely, for BD, there were no statistically significant differences between "BD with cognitive dysfunction" and "BD without cognitive dysfunction" with regard to any of the socio-demographic variables taken into account.

Cognitive performance after clinical remission

At time of clinical remission, the mean MoCA total score in the sample was 25.94±2.60. In patients diagnosed with MDD the mean score was 25.81±2.65 while it was 26.22±2.50 in patients with BD. Therefore, patients with MDD were on average below MoCA threshold of normality, whereas patients with BD showed normal levels. However, this difference was not statistically significant (U=1188.0, Z=-0.930, p=0.353) nor clinically relevant, in our opinion.

Scores for the single cognitive domains of the MoCA at remission and comparison between MDD and BD are reported in Table 4.

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Change in cognitive performance from depression to remission

All subjects enrolled in the study showed some improvement in the overall cognitive performance between depression and remission. There was indeed a statistically significant change in MoCA score both in the group of patients with MDD (Z=-7.326, p<0.001) and in the group with BD (Z=3.773, p<0.001).

Taking into consideration the single MoCA domains separately, in MDD patients there was a statistically significant improvement in the domains of Memory (Z=-4.273, p<0.001), Executive Functions (Z=-3.431, p=0.001) and Attention (Z=-2.389, p=0.017), while there was no statistically significant variation in the domains of Visuospatial Abilities (Z = -0.576, p = 0.564), Verbal Fluency (Z=-1.531, p=0.126) and Orientation (Z=-0.401, p=0.688).

Likewise, in BD patients, there was a statistical significant variation in Memory (Z=-3.559, p<0.001), Executive Functions (Z=-3.431, p=0.001) and Attention (Z=-2.234,

p=0.020), while no significant changes were found in any other domain: Visuospatial Abilities (Z=-0.530, p=0.596), Verbal Fluency (Z=-1.554, p=0.120) and Orientation (Z=-1.734, p=0.083).

Considering only patients with initial cognitive dysfunction (MoCA <26 in depressive phase), a statistically significant improvement of MoCA score was observed both in MDD (Z=-5.113, p<0.001) and in BD subjects (Z=-3.730, p<0.001). However, the mean value at the time of clinical remission was lower than the normal cut-off of the MoCA both in MDD and BD (24.54±2.53 and 25.36±2.75, respectively), suggesting a residual cognitive dysfunction in subjects with initial impairment.

Correlations between cognitive performance and clinical-demographic variables

One objective of our study was to search for correlations between cognitive performance and demographic and clinical variables, in a naturalistic sample representative of patients accessing specialized care for mood disorders.

During depression, the MoCA score in the total sample was negatively correlated with HDRS (ρ=-0.474, p<0.001), but not with HARS score (ρ=0.064, p=0.708). Furthermore, the MoCA score was negatively correlated with DUI (ρ=-0.240, p=0.012). No other significant correlations emerged with the main demographic and clinical variables: age (ρ=-0.197, p=0.243), age of onset (ρ=-0.145, p=0.392), duration of illness (ρ=-0.007, p=0.966) and number of episodes of illness (ρ=-0.006, p=0.971).

At remission, MoCA score was negatively correlated to three clinical variables: age (ρ=-0.313, p=0.001), HDRS score during depression (ρ=-0.365 p<0.001) and DUI (ρ=-0.266, p=0.005).

During depression, MoCA score correlated with HDRS score both in patients with MDD (ρ=-0.382, p=0.001) and BD (ρ=-0.657, p<0.001), with no statistically significant differences between two groups (z=1.33, p=0.18). The MoCA score was also correlated with DUI (DDM: ρ=-0.237, p=0.045; DB: ρ=-0.462, p=0.004) without significant differences between the two groups (z=1.09, p=0.28). Furthermore, no other significant correlations emerged between global cognitive performance and specific demographic and clinical variables in the two separate groups.

The DUI was not significantly correlated with any of the six cognitive domains, except with orientation in bipolar patients (ρ=-0.473, p=0.003).

Finally, even performing the same analyses separately for patients with (MoCA <26 during depression) versus without cognitive impairment, no statistically significant correlations emerged between DUI and single domains of the MoCA in unipolar nor in bipolar depression.

Discussion

Consistently with literature, the results of our study confirmed that patients suffering from depression, regardless of longitudinal diagnosis, are characterised by concomitant mild cognitive impairment. In our sample, more than 1 out of 2 depressed patients scored lower than normal on the MoCA screening, indicating the presence of a mild cognitive impairment. This result is in line with previous studies that have shown a prevalence of cognitive impairment around 25-50% of MDD cases(Gualtieri & Morgan, 2008), even though the real prevalence of cognitive symptoms in depression is not fully clarified yet(Douglas et al., 2018; Trivedi & Greer, 2014). In a recent publication, during depressive episodes, Douglas and colleagues found prevalence rates of 14.7-

52.9% and 32.2-64.4% in outpatients with MDD and BD respectively, depending on the definition of cognitive impairment considered(Douglas et al., 2018) and, therefore, substantially in line with our results.

In this study, we also sought to investigate the clinical features associated with cognitive impairment in MDD and BD in a naturalistic context. Our study confirmed that a greater severity of depressive symptomatology is associated with a worse cognitive performance. This association is well established and was reported by McDermott and colleagues in a meta-analysis indicating a specific correlation between depression severity and episodic memory, executive functions and information processing speed(McDermott & Ebmeier, 2009) and, more recently, in a study comparing the cognitive function of MDD and BD patients(Bo et al., 2018). In our study, however, the severity of depressive symptomatology was not associated with any specific domain, either in MDD or in BD. This difference could be due to the lack of sensitivity of the MoCA in highlighting alterations of single domains, compared to its good sensitivity in relation to the overall performance.

If the presence of a relationship between severity of depression and cognitive impairment has been already reported, the relationship between DUI and cognitive impairment during depression represents a novel finding emerging from our study. DUI is a clinical variable of great interest in clinical practice because, unlike many other factors, it is modifiable by providing early diagnosis and treatment to the patient. It is well established that a prolonged DUI is associated with a poorer outcome not only in schizophrenia(Buoli et al., 2013), but also in mood disorders(Altamura et al., 2007), anxiety disorders(Altamura, Dell'osso, D'Urso, et al., 2008; Dell'Osso, Camuri, Benatti, Buoli, & Altamura, 2013) and obsessive-compulsive disorder(Dell'Osso, Buoli,

Hollander, & Altamura, 2010). In our study, the average DUI was lower than that reported by most studies in the field, but consistent with the constant reduction of DUI over epochs of time observed in recent reports(Dell'Osso et al., 2016)~~(Dell'Osso et al., 2017, 2016)~~. Of note, present findings indicate that a prolonged DUI is also associated with a worse cognitive performance during depression. Hypothetically, this may represent one of the mechanisms through which depressed and bipolar patients, belatedly treated, experience a worse long-term outcome. Particularly in BD, this association is more consistent (the correlation value was greater in bipolar than in unipolar depression), probably since the onset of BD tends to occur in late childhood or early adulthood(Duffy, 2000) and more time can elapse before a correct diagnosis is formulated and an appropriate treatment prescribed(Goldberg & Ernst, 2002).

In our study, not only during depression but even after remission, DUI was correlated with cognitive impairment: this result could reflect another detrimental effect through which DUI determines a poorer outcome in mood disorders. This might be summarized as follows: the longer the DUI, the higher the residuality of cognitive deficits after depression in mood disorders.

One of the main objectives of our study was to highlight the distinctive features of unipolar and bipolar depression from a cognitive perspective, as, to date, evidence in this field is still limited and inconclusive. Our results highlighted similar patterns of cognitive impairment in unipolar and bipolar depression, quantitatively in terms of severity and qualitatively in terms of profile of cognitive domains involved. This result is also consistent with available evidence. Bearden and co-workers, for instance, showed overlapping patterns of cognitive impairment in unipolar and bipolar patients, which did not appear secondary to clinical status but rather related to a common

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pathophysiological genesis, suggestive of temporal lobe dysfunction (Bearden et al., 2006). Subsequently, Hermens and colleagues analysed the neurocognitive profiles of unipolar and bipolar patients in early age, demonstrating similar deficits primarily referred to verbal memory impairment(Hermens, Naismith, Redoblado Hodge, Scott, & Hickie, 2010). More recently, Daniel and co-authors (2013) showed that neurocognitive performance did not differentiate patients affected by MDD from those suffering from BD-I(Daniel et al., 2013). Similar neurocognitive alterations have also been reported by Xu and colleagues (Xu et al., 2012) and, previously, by Sweeney and co-workers (Sweeney, Kmiec, & Kupfer, 2000). Indeed, in our opinion, the present study has the merit of having enrolled unipolar and bipolar patients during acute depressive episodes, whereas the cited studies enrolled rather heterogeneous samples of bipolar patients, consisting of mixed depressed, manic and euthymic patients. Furthermore, the sample sizes of some of the abovementioned studies were smaller than our sample and, consequently, the results less generalizable.

It is noteworthy to mention another significant difference of our study compared to those available in literature. To date, cross-sectional studies on cognition in unipolar and bipolar depression have been using extensive batteries of neuropsychological tests, while in our study we used a quick and easy cognitive screening test for daily clinical practice. Although the assessment through neuropsychological tests is preferable for a more exhaustive analysis of patients' cognitive impairment, we believe the results of the present study reiterate the usefulness of the MoCA as a screening tool in daily clinical practice, in order to estimate the degree of cognitive impairment associated with depression.

Our results should be interpreted in light of the following limitations. First of all, one possible limitation lies in the lack of a control group of healthy subjects to allow for comparison analyses with patients with MDD and BD. Moreover, the naturalistic context in which the study was conducted determined the enrollment of two groups of patients that, although homogeneous for most of the clinical-demographic variables, had some peculiarities due to the different course and to the different treatment patterns. To date, the effect of drug therapy on cognitive functions is still uncertain due to the limited number of studies on this topic (Senturk Cankorur, Demirel, & Atbasoglu, 2017). Metanalytic evidence suggests that antidepressants have positive cognitive effects on psychomotor speed and on delayed recall (Rosenblat, Kakar, & McIntyre, 2015). Conversely, antipsychotics have generally been imputed detrimental effects on cognition, although controversies between experts in this field still remain (Donaldson, Goldstein, Landau, Raymont, & Frangou, 2003; Frangou, Donaldson, Hadjulis, Landau, & Goldstein, 2005; Glahn et al., 2007; Martinez-Aran et al., 2008).
Furthermore, the widespread use of poly-therapies in the BD (and in part in MDD) makes it difficult to estimate the impact of any single drug on cognition. In our study, however, we conducted some sub-analyses to overcome these biases, excluding between groups differences and within diagnostic medication-dependent cognitive variability.
The correlational design of the study may also be considered as a limitation as well as the lack of ~~,~~control for group differences in number of rates of hospitalizations and number of previous mood episodes. Finally, the sample size of our study was relatively small, which is why further clinical trials on larger samples are warranted to confirm the evidence that emerged from our study.

In conclusion, patients with MDD and BD had similar rates and patterns of cognitive impairment during depression, both in terms of severity and alterations of specific cognitive domains, that particularly affect executive functions and memory. The severity of cognitive deficits was related to the severity of depressive symptomatology and tended to improve with remission of depressive symptoms. Nonetheless, patients with greater cognitive impairment during depression had residual cognitive deficits after remission.

DUI could represent a key factor in determining cognitive impairment during depressive episodes, as patients for whom appropriate treatment was delayed experienced greater cognitive impairment than those promptly treated. The relationship of cognitive impairment with the DUI seemed to be particularly (but not only) significant for BD.

Keypoints

- Although distinct entities, unipolar and bipolar depression determine similar patterns of cognitive impairment in terms of severity and types of altered domains.
- Depression (but not anxiety) severity is associated with cognitive performance in depression.
- Prolonged duration of untreated illness is associated with more severe cognitive impairment during depression, particularly but not specifically in bipolar disorder.

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Declaration of interests statement

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Author contributions

CG: conceived and designed the study, participated into the acquisition of the data, performed statistical analyses and drafted the manuscript, tables and figures; MV and FG performed the acquisition of data; MFB contributed to the conception and design of the study and participated into the acquisition of data; BD edited the final manuscript, tables and figures; CAV: supervised the study and contributed to the revising the manuscript.

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TABLES

Table 1. List of inclusion and exclusion criteria

Inclusion criteria
Male or female gender
Age>18
Diagnosis of major depressive episode (MDE)
Longitudinal diagnosis of major depressive disorder or bipolar disorder I or II according to DSM-5 criteria
Exclusion criteria
Diagnosis of Mixed Episode and/or subthreshold manic symptoms
Clinically relevant learning or reading disability, dyslexia, illiteracy
Diagnosis of cognitive disorder
History of moderate to severe head injury
Uncontrolled thyroid dysfunction
Recent alcohol or substance abuse
Concomitant therapy with high dose anticholinergics
Concomitant therapy with benzodiazepines at a dosage equal or higher than diazepam 7.5 mg/day
Electroconvulsive therapy within 6 months

Table 2. Socio-demographic characteristics of the sample divided in two diagnostic groups

	MDD	**BD**	**p**
Sample size	72	37	
Gender, f%	65.3%	70.3%	.600
Age, mean±SD	56.24±14.51	56.89±10.02	.602
Marital status, %			
Unmarried	15.3%	27.0%	.111
Married	62.5%	59.5%	
Divorced	11.1%	7.3%	
Widow	11.1%	6.2%	
Education, %			
Primary school	9.7%	8.1%	.904
Secondary school	6.4%	21.6%	
High school	41.7%	48.6%	
University	22.2%	21.6%	

Employment status, %			
Unemployed	20.8%	27.0%	.744
Employed	41.7%	32.4%	
Retired	37.5%	40.5%	
Nationality, italian %	93.1%	97.3%	.358

Abbreviations: MDD, Major Depressive Disorder; BD, Bipolar Disorder; SD: standard deviation.

Table 3. Clinical characteristics of the sample divided in two diagnostic groups

	MDD	**BD**	**p**
Family history for psychiatric disorders, % positive	63.9%	75.7%	.212
Age at onset, mean±SD	34.15±14.94	30.0±12.89	.224
DUI) in months, mean±SD	59.81±84.43	63.51±73.33	.074
Duration of illness in years, mean±SD	22.22±13.59	26.89±12.10	.087
Psychiatric comorbidities, %	27.6%	13.5%	.091
Comorbidity with personality disorders, %			
None	76.4%	73.0%	.463
Cluster A	1.4%	5.4%	
Cluster B	13.9%	10.8%	
Cluster C	5.6%	2.7%	
Not specified	2.8%	8.1%	
Medical comorbidities, % present	48.6%	40.5%	.389
History of psychosis, positive %	19.4%	27.0%	.361
History of alcohol abuse, positive %	5.6%	13.5%	.153
History of substance abuse, positive %	11.1%	2.7%	.131
Number of episodes of illness, mean±SD	3.38±1.84	5.57±3.33	**.001**
Duration of current MDE, days	77.43±34.85	84.32±37.84	.382
Previous hospitalizations, yes %	22.2%	59.5%	**<.001**
Previous suicide attempts, yes %	26.4%	45.9%	**.030**
Psychopharmacological treatment			
Antidepressants, %	93.1%	75.7%	**<.001**
Antipsychotics, %	34.7%	59.5%	**.019**
Mood stabilizers, %	4.2%	40.5%	**.004**
Benzodiazepines, %	66.7%	56.8%	.295

Abbreviations: MDD, Major Depressive Disorder; BD, Bipolar Disorder; DUI, Duration of untreated illness; MDE: Major Depressive Episode; SD: standard deviation.

Table 4. Mean scores of MoCA single domains during depression and remission.

		DEPRESSION			REMISSION		
	Maximum values	**MDD**	**BD**	**p**	**MDD**	**BD**	**p**
Memory	5	2.35±1.71	2.32±1.58	.902	3.36±1.24	3.43±1.09	.837
Visuospatial abilities	4	2.81±1.15	2.89±1.27	.514	2.90±0.92	3.00±0.94	.543
Executive functions	4	2.85±1.08	2.70±1.31	.679	3.49±0.69	3.57±0.65	.541
Attention	6	5.40±0.93	5.30±1.24	.823	5.69±0.62	5.70±0.66	.908
Verbal fluency	6	5.01±1.11	5.11±0.94	.862	5.21±1.03	5.38±0.83	.589
Orientation	6	5.81±0.60	5.68±0.63	.126	5.75±0.73	5.89±0.32	.393
MoCA total score	30	24.11±4.04	23.89±3.78	.709	25.81±2.65	26.22±2.50	.353

Abbreviations: MDD, Major Depressive Disorder; BD, Bipolar Disorder; MoCA, Montreal Cognitive Assessment.