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ARCHIVES OF
Depression and Anxiety

ISSN: 2455-5460 DOI: https://dx.doi.org/10.17352/ada

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Received: 25 November, 2019
Accepted: 16 December, 2019
Published: 17 December, 2019

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Keywords: Bipolar disorder; Cognition; Cognitive impairment; Neuroimaging; Quality of life

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Review Article

Cognitive impact in bipolar disorder

Abstract

It appears that bipolar patients suffer from cognitive difficulties whereas they are in period of thymic stability. These intercritical cognitive difficulties are fairly stable and their severity is correlated with the functional outcome of patients. Nevertheless, the profile of cognitive impairment varies significantly from study to study quantitatively and qualitatively. According to the studies, the authors find difficulties in terms of learning, verbal memory, visual memory, working memory, sustained attention, speed of information processing, functions executive. On the other hand, deficits of general intelligence, motor functions, selective attention, and language are not usually found. One of the reasons for the heterogeneity of results is the difficulty of exploring cognition in bipolar disorder. Many factors must be taken into account, such as the presence of residual mood symptoms, the longitudinal history of the disorder (age of onset, number of episodes due, among others, the neurotoxic impact of depressive episodes and deleterious cognitive effects). (length of hospitalization), level of disability severity, comorbidities (particularly addictive).

Introduction

Cognitive impairment is mainly responsible for disability in bipolar disorder [1,2]. Based on this finding, studies have looked at the cognitive profile of patients with bipolar disorder. Are there any cognitive impairments inherent in bipolar disorder that could be explained by the pathophysiology of the disease? It would seem that different cognitive profiles are identified rather than a single profile, although the alteration of executive functions and verbal memory are frequently found in studies. The functions reached seem to depend on the characteristics of the disorder (predominant polarity of the disorder etc.) and the attack would be evolutionary in time [3]. In the present paper, the impact of the pharmacological treatment on cognitive function is not mentioned because it seems difficult to evaluate.

Pathophysiology of bipolar disorder and cognitive disorders

At the cellular level, the pathophysiology of bipolar disorder would involve increased intracellular sodium and calcium levels resulting from impaired Na/KATPase pump [3]. At the neuronal level, it results from this increased intracellular concentration of positive ions, an increase in the excitability of the neuron and the modulation of the release of excitatory neurotransmitter such as glutamate and dopamine. There would also be a decrease in the plasma level of the inhibitory neurotransmitter GABA. This would result in an increase in excitatory neurotransmissions and a decrease in inhibitory neurotransmissions. The neurotoxicity of the thymic episodes inherent in bipolar disorder is now recognized [4]. Each episode leads to oxidative stress responsible for DNA damage and a decrease in transcription of a neurotrophic factor, the Brain-Derived Neurotrophic Factor (BDNF). This results in neuronal atrophy, partly responsible for the cognitive impairment seen in patients with bipolar disorder. Advanced mood disorders would be associated with an alteration of cellular resilience and brain plasticity, causing psychosocial dysfunction found in these patients [5]. A growing body of research suggests an association between neuroinflammation and cognitive dysfunction in bipolar disorders, such as schizophrenia and certain neurodegenerative disorders such as Alzheimer's disease [6]. Some post-mortem studies have found a high level of microglial activation markers in the frontal cortex of patients with bipolar disorder suggesting that microglia, a macrophage tissue of the brain parenchyma, play a role in the pathophysiology of the bipolar disorder [7].

A study whose initial hypothesis stipulated a negative association between high levels of inflammatory markers of cerebrospinal fluid and executive functions in bipolar disorder [8]. It was evaluated the association between five cognitive domains and neuroinflammatory markers, taking into account the type of bipolar disorder and treatments, in euthymic patients. The authors then repeated these regression models in controls matched to patients on age and sex. Their hypothesis proved correct. The cerebrospinal levels of all inflammatory markers (YKL-40, TIMP1, MCP-1, sCD14) were significantly higher in the patients. Cognitive performance (executive functions, verbal functions, visuospatial functions, attention/speed of treatment) was significantly lower in patients. Inflammatory markers, after adjusting for covariates, accounted for 42.8% of

Citation: Bourin M (2019) Cognitive impact in bipolar disorder. Arch Depress Anxiety 5(2): 052-058. DOI: https://dx.doi.org/10.17352/2455-5460.000042

impaired executive function in patients with bipolar disorder. Of these markers, only the YKL-40 microglial marker was individually and significantly associated with the performance of executive functions with a large effect size. Attention and processing speed were also significantly related to a high level of markers without any markers being individually associated with this disturbance. The results could not be replicated in control subjects suggesting that neuroinflammatory markers have a pathophysiological role in altering executive functions in patients with bipolar disorder. In a meta-analysis [9], relied in particular on the work which compared psychometric tests corresponding to different brain areas in patients suffering from bipolar disorder [10] and control subjects, and thus deduced the neuronal circuits. preferentially altered in the disease. They suggest that abnormalities of the ventral prefrontal cortex and anterior cingulate gyrus, anatomical structures associated with executive functions such as response inhibition, may have an etiological role in bipolar disorder. Similarly, alterations of the dorsal prefrontal cortex, a structure associated with mental flexibility, constitute the endophenotype of bipolar disorder. Another endophenotypic trait widespread in bipolar disorder would be a verbal memory deficiency, a marker of a frontotemporal and fronto limbic dysfunction [11].

Neuroimaging studies in bipolar disorders associated with cognition

The most convincing result in terms of structural imaging is the combination of a lithium treatment with an increase in the volume of gray matter in the areas involved in the emotions (amygdala, hippocampus, anterior cingulate gyrus), whereas an anticonvulsant therapy was not [12]. Few significant associations emerged from functional imaging; the interpretation of the results being limited by the small size of the samples "treated" vs. "untreated". Significant effects of drug treatment were more frequently observed in prospective studies focusing on the BOLD signal, the effects tending to towards normalization, i.e. the neurofunctional activity of patients suffering from bipolar treated approached that of control subjects. A literature review of publications published from 1990 to 2008 listed studies from the National Center for Biotechnology Intervention (NCBI) dealing with abnormalities in anatomical, functional and glutamatergic neuroimaging identified in bipolar disorders [12]. The most important neuro-anatomical-functional variations identified between subjects with bipolar disorder and control subjects were at the thalamus and hippocampus level. From this study is was pointed out:

- A tendency to the absence of hippocampal volume variation once the bias of the chemotherapy is taken into account (15 studies carried out between 1992 and 2007 did not find any significant difference in terms of hippocampal structure/volume between patients and controls whereas 5 studies performed between 1992 and 2008 found a decrease in hippocampal volume in patients and 4 studies conducted from 2004-2008 an increase).

- Abnormal activation of the limbo-thalamocortical pathway. The authors could not clearly interpret this result, as some studies explain the hypermetabolism regained as an activation "effort" necessary for patients to achieve the same memory and cognitive-social performance as witnesses to emotional stimuli and others. explaining by a real better basic memory capacity.

- A dysactivity of the glutamatergic receptors at the level of the hippocampal and thalamic region and an abnormal activation of glutamatergic neurotransmission, resulting from a genetic polymorphism within the receptors and/or transporters of glutamate expressed within these regions and/or a dysregulation of Glu/Gln glutamate degradation cycle in glial cells. In parallel, GABAergic receptors dysactivity and inhibition of GABAergic neurotransmission are associated.

- No fixed neuroanatomical lesion or biosynthesis deficit was found. neurotransmitters, but complex abnormalities of regulation within the channels and neural circuits.

Initial and progressive cognitive profile in bipolar disorders

Attention, verbal memory and executive functions would represent cognitive functions in patients with bipolar disorder. Verbal fluency and visual memory would be preserved. Several studies suggest that a deficit in verbal memory is the most frequently found in relatives of a patient with bipolar disorder. So, Bora and al, in their 2009 meta-analysis, compared the cognitive performance of patients presenting with euthymic phase, or first-degree relatives of patients with a bipolar disorder, with control subjects, in order to identify the basic cognitive profile of bipolar disorder evolution and some confounding factors such as medication. The authors defined a cognitive endophenotype of bipolar disorder by altering verbal memory and two functions the inhibition and mental flexibility, the inhibition disorder representing the cognitive trait the more constitutive of this endophenotype [9]. Alterations in treatment speed and visual memory, although found in the clinical expression of bipolar disorder, are not present in relatives and thus do not appear to be related to genetic susceptibility inherent in bipolar disorder.

Another study compared the cognitive profile of three groups of patients with bipolar stable euthymic disorder divided according to their treatment (lithium group, n=29, lithium group and one or more anticonvulsants, n=28, group one or more anticonvulsants, n=16). All three groups were comparable and did not differ significantly in age, subtype of bipolar disorder, previous episodes and hospitalizations. A group of 25 healthy control subjects were also included. The cognitive tests performed in this study found in all three euthymic patient groups a significant alteration of executive functions, including inhibition, and social cognition with impaired emotion recognition [14]. Alteration of these functions would therefore be inherent in bipolar disorder regardless of the chemotherapy used. The authors pointed out other factors than chemotherapy (the taking of toxic drugs, for example) not taken into account

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in their study and which constituted biases, which may also be responsible for cognitive disorders in bipolar disorders. This notion of impairment of cognitive functions inherent in the disorder was already assumed in 2007 by the authors of a comparative study of cognitive functions between patients suffering from bipolar disorder treated with monotherapy and control subjects [15]. This team of researchers compared the psychometric test results of a group of 17 patients with lithium-treated euthymic bipolar disorder and a group of 11 patients with euthymic bipolar disorder treated with valproate and a group of 29 control subjects. They used three subtests of the WCST to measure mental flexibility and training concepts, the Weschler Memory Scale (WMS) to measure verbal memory and three subtests of the WAIS-R to measure working memory, processing speed and visuospatial capabilities. Patients had to be in clinical remission treated with either monotherapy for at least one month and the absence of decompensation was ensured by low scores (<10) on depression scales (HAMD) and mania (YMRS). Groups were similar in terms of sex, education level, duration and severity of illness, but not age (patients treated with lithium were significantly older). The similarity of the groups in terms of pre-morbid cognitive level was ensured by one of the WAIS-R subtests. A multivariate analysis of covariance was applied by integrating these seven variables "scores" and the covariate "age". The only significant difference found was verbal memory assessed at the WMS, which performed significantly lower in both groups of patients compared to the control group with an estimated effect size of 0.17 and p=0.02. There was no significant difference in performance between the two treatment groups regarding verbal memory, nor any influence of age on the WMS. There was no significant difference between the three groups regarding other cognitive functions. This would suggest that either the alteration of verbal memory is intrinsic to bipolar disorder, or that the two mood stabilizers alter cognitive function in the same way. The authors remain aware of the biases of their study (cross-sectional study on small samples).

A review of the literature published in 2011 proposed a staging of bipolar disorder, including a model of the evolution of bipolar disorder segmented into four progressive stages of the disease according to out-of-episode residual thymic symptoms, cognitive functioning, and biomarker levels [16]. Stage 1 would be a cognitive-free stage with a high level of TNF alpha. Stages 2, 3 and 4 would have a low level of BDNF, stage 3 with cognitive and functional deterioration and stage 4 lack of autonomy. However, there is no significant difference between the very early and late stages of the disease in cognitive function [16]. The interest of a staging of bipolar disorder lies in the identification of individuals at high risk of developing the disease and in the therapeutic benefit that would be provided by very early management of the disease. It would also allow better therapeutic indications, the different stages corresponding to different needs and able to respond to treatments in a differentiated way.

Bipolar disorders are recognized as heterogeneous, and the variability of symptoms extends to cognitive domains. This heterogeneity of the disorder, observed daily in the psychiatric exercise, is recalled by the International Society for Bipolar Disorders (ISBD) [17]. ISBD identifies altered cognitive domains in bipolar disorders similar to those in schizophrenia but in a less severe manner. It also suggests cognitive characteristics common to bipolar disorders, including a consequent deficit in the Hayling Sentence Completion Test (HSCT, test measuring executive functions and specifically inhibition). Similarly, the ISBD literature review reports a similar disability to that seen in patients with schizophrenia at the Cambridge Neuropsychological Test Automated Battery Intradimensional/Extra-Dimensional Set-Shifting Task (CANTAB IDED, Evaluating Mental Flexibility) and a moderate deficit compared to the London Tower test takers (assessing planning). Inhibition, mental flexibility and planning would be behavioral manifestations underpinned by common biological mechanisms related to the functioning of the ventral prefrontal cortex. This could be dysfunctional in patients with bipolar disorder. ISBD members complain that these tests (HSCT/CANTAB IDED/Tower of London) are missing from meta-analyzes of cognition in bipolar disorder because of the small number of studies that have used them. Finally, the ISBD resumes the results of the study by Bora, et al., [9], suggesting that the cognitive deficits observed both in patients and their relatives in the first degree who do not suffer from bipolar disorder partly reflect a diathesis of genetic origin of the disease. Another team found underperformance in three groups of patients with bipolar disorder (euthymic, depressive, manic or hypomanic) compared to the control group for these same cognitive domains (executive functions and verbal memory) [18]. We will return to this study in the following paragraph. In summary, bipolar disorder is thought to be associated with cognitive disturbances that worsen as the course of the disease progresses, probably resulting from both neurodevelopmental and neurodegenerative processes, in the areas of attention, verbal memory and executive functions.

Cognitive profiles and features of bipolar disorder

Cognitive impairment and age of reporting bipolar disorder: The meta-analysis of Bora, et al., [9], presented above shows more marked cognitive impairment in early-onset bipolar disorder: a young age entry into the disease was associated with a verbal memory deficit and a slowdown psychomotor more important (meta-regression analysis, Verbal Learning: SE=0.02, p=0.027, 15 studies; Trail Making Test-A: SE=0.02, p=0.0014, 14 studies).

Conversely, a study in elderly patients with bipolar disorder found poorer cognitive performance in patients whose disorder started later [19]. It included two groups of patients over age 60, distinguished by age entry into the disease that was less than or greater than 40 years, as well as a control group. Compared in the control group, the group with an early age of onset was worse performance only in the areas of verbal memory and executive functions, while that the late-onset age group showed more severe disturbances in all areas. The study concluded that there is probably a more severe impairment of cognitive function in elderly patients entered late in bipolar illness. Groups were not significantly differing on traditional

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confounders (medication, number of hospitalizations, etc.). The authors emphasized the importance of age-related neurodegenerative factors (cognitive decline inherent in age) that may have interfered with the cognitive process in patients who developed delayed bipolar disorder, which could explain the extent of the cognitive domains affected in this group, as well as the small size of their patient samples (20 patients in each group). The age of entry into bipolar disorder may explain the heterogeneity found in elderly patients with bipolar disorder. Martínez-Arán, et al., did not find an association significant age difference between bipolar disorder and cognitive impairment [18].

Cognitive impairment and severity of bipolar disorder: Clinical observation suggests that the severity of cognitive impairment may depend on the severity and number of episodes patients experience. In 2004, a study by Martinez-Aran, et al., investigated the links between characteristics of bipolar disorder and cognitive impairment in a group of 40 euthymic patients on drug treatment recruited by Barcelona's Disorders Program at Hospital Clinic and a group of 30 control subjects [18]. The exclusion criteria were essentially substance abuse and neurological history. The research team focused on cognitive functions deemed deficient in bipolar disorders: attention, verbal memory and executive functions, evaluated by frequently used psychometric tests (Stroop test, WAIS, TMT, CVLT, WCST and Controlled Oral Word Association Test). The performance of verbal memory tasks was significantly associated with the number of manic episodes and the number of hospitalizations. The alteration of the executive functions was significantly correlated with the duration of the disease. The psychotic symptoms found in the history of the disease were significantly associated with greater disturbances of verbal memory with worse results at the CVLT. Thus, the average performance on the learning task of the CVLT was 43.0 (standard deviation SD 11.6) in patients with a history of psychotic symptoms compared to an average of 52.5 (SD 11.8) in patients without a history of psychotic symptoms. Mean performance scores for two other CVLT tasks, free recall and index recall, were also lower in patients with a history of psychotic symptoms (free recall: 8.9±3.6 versus 11.9±3.7, subscripted boost: 9.7±3.1 versus 12.4±2.9).

In 2016, Cullen, et al., published a review of the literature examining the prevalence of cognitive impairment in bipolar disorder and associated factors [20]. The included population included subjects with bipolar disorder and euthymia. The prevalence found for cognitive disorders were (threshold of cognitive deficit set at the 5th percentile): between 5.3 and 57.7% for executive function disorders; between 9.6 and 51.9% for attention deficit and working memory disorders; between 23.3 and 44.2% for the disorders of the treatment speed and the reaction time; between 8.2 and 42.1% for verbal memory disorders; between 11.5 and 32.9% for visual memory disorders. This synthetic article found a significant positive association between cognitive deficit and certain characteristics of the disorder: duration of illness, number of manic episodes, residual mood symptoms, number of hospitalizations. The majority of articles found no significant association between psychotic features of thymic episodes and cognitive impairment. Socio-demographic characteristics such as socio-economic environment and premorbid cognitive abilities were often considered as adjustment factors between groups and were not analyzed separately.

Cognitive disorders and polarity of thymic episodes in bipolar disorders: Would the mood symptoms, according to their depressive or manic polarity, be more or less deleterious for the cognitive functioning of the individual with bipolar disorder? The review of Cullen, et al., [20], presented in the previous paragraph found a positive association between cognitive impairment and number of manic episodes in five out of twelve studies while a positive association with the number of depressive episodes was identified than by two studies out of eleven.

Martinez-Aran, et al., were specifically interested in the link between cognitive disorders and polarity of thymic episodes [21]. The included population consisted of three groups of patients: patients with depressive phase (n=30), patients in the manic phase (n=34), patients in the euthymic phase (n=44), and a group of witnesses (n=40). The DSM-IV criteria and the Hamilton and Young scales were used to define bipolar disorder and the polarity of the current episode, respectively. The tests used and the cognitive functions evaluated were the same as in the previous article, with an evaluation of the visual memory. A multivariance analysis (MANOVA) was used to compare the neuropsychological performances between the four groups followed by a post hoc test of Tukey when a significant effect was found (p significant <0.05). The three groups of patients had significantly lower performance than the control group in the areas of verbal memory and executive functions.

The "depression" and "euthymia" groups had significantly greater alterations than the attention controls (Trail Making Test-A, p=0.009), unlike the "mania" group. Only groups in the depressive or manic phase had significantly impaired performance compared to non-verbal memory and recognition system controls (evaluated by the visual and logical memory sub-tests of the Wechsler Memory Scale-Revisited). In the euthymic phase, there was no significant difference with the control group for these tests. The authors thus suggested the alteration of complex memory processes in patients in remission. Only manic polarity was significantly associated with cognitive dysfunction in verbal memory, essentially represented by the California Verbal Learning Test. Depressive polarity was not significantly associated with cognitive dysfunction. The manic polarity thus seems deleterious for the cognitive functioning. A neurotoxic effect of the manic state could be explained by the hyper-cortisolemia associated with this clinical state. Some studies cited by Martinez-Aran, et al., [21], related memory dysfunction to symptoms depressive residuals, had many biases with a non-representativity of samples in particular. The Martinez-Aran, et al., study also linked suicide attempts and verbal memory impairments: the correlation coefficient of Pearson (r) showed an association between the CVLT deficit and the number of suicide attempts: -0.15<r<-0.33 subtests of the CVLT, with significant p:

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0.01<p<0.05. ISBD reported five studies comparing the emotional decision-making of patients with bipolar disorder in the manic phase and depressive phase in control subjects [17]. The test used was the Cambridge Gamble Test (CGT), which assesses the patient's ability to estimate their odds of betting game. All of these studies showed that patients, regardless of the polarity of the episode current, had a capacity to estimate the defective risk. They increased their earnings more slowly as the witnesses, while the chances of winning became more favorable. Regardless of the thymic state of the patient, the decision-making function was reached. Thus, the majority of the studies mentioned above show that recovering a euthymic state after an episode does not resolve all cognitive disorders. In summary, the disturbances would tend to increase with: duration of illness, number of hospitalizations, number of manic episodes, psychotic symptoms.

Cognition and psychiatric comorbidities associated with bipolar disorder

The same patient often presents with several intricate psychiatric pathologies and it is sometimes difficult to distinguish the symptoms of the different disorders as we are forced by the categorical approach to psychiatric pathologies. The lifetime prevalence of comorbidities in patients with bipolar disorder type 1 is greater than 50% [22]. Bipolar disorders include frequent comorbidities, anxiety disorders and substance use disorders, as well as attention deficit disorder with or without hyperactivity (ADHD).

The isolated impact of anxious comorbidity on the cognitive functioning of patients with bipolar disorder is not known. However, this comorbidity would be a factor of poor prognosis in bipolar disorder [24]. Anxiety disorders are thought to be associated with the severity of bipolar disorder and may be involved in cognitive dysfunction. Among the psychiatric pathologies of Axis 1 of the DSM IV, bipolar disorder is associated with the highest lifetime prevalence (almost 50%) of substance use disorders. In a review of the literature, Balanza-Martinez, et al., examined the links between substances and cognitions in these patients [24]. They point out from the outset their difficulty in studying these links: in many comparative neuropsychological studies conducted in groups of patients suffering from bipolar disorder, substance use disorders are exclusionary factors precisely because they are considered confounding factors. Some studies on alcohol exist however such as the study of Levy, et al., published in 2008 [25]. Levy and his team compared three groups of patients with bipolar disorder: a group meeting the DSM-IV criteria for alcohol dependence in the last six months, a group meeting the criteria for alcohol dependence in remission (abstinence for at least 12 months) and a group of patients without substance use disorder or past, according to the criteria of the fifth version of the Addiction Severity Index. The two groups currently having or having had alcohol dependence in the past had significant alterations in executive function (WCST and Stroop test) compared to the control group. The group with the current comorbidity alcohol also exhibited a significant impairment of verbal and visual memory compared to the control group. The group with comorbidity alcohol in remission exhibited overall cognitive abilities (measured by Wechsler-scale estimates of Intellectual Quotient) lower than the control group (mean difference of 10.88, SD 4.70, p<0.01) but also lower than the active alcohol comorbidity group (mean difference of 11.49, AND 3.99, p<0.006). A possible confounding factor is worth noting; there was a greater disability in the two groups currently having or having had alcohol dependence in the past compared to the control group. However, this factor could be the consequence of cognitive dysfunction itself associated with comorbidity alcohol, current or in remission. It should also be noted that these two groups also contained patients with abuse (active or past, found on inclusion in the Addiction Severity Index) of other substances (marijuana...). The study by Levy, et al., thus emphasizes that the dual diagnosis of alcohol dependence and bipolar disorder would aggravate the cognitive deficit already associated with bipolar disorder.

In adolescents and young adults, it is sometimes difficult to distinguish between bipolar disorder and attention deficit disorder with or without hyperactivity (ADHD), whose diagnostic criteria are close to: thus, it is sometimes difficult to distinguish the criteria DSM-IV "distractibility" and "increase of the activity and energy" of the bipolar disorder of the criteria "inattention, often has difficulty to keep his attention at work or in the games And "hyperactivity" of ADHD. Moreover, when the distinction is made, the two disorders are frequently comorbid. Some studies do not find any difference in performance regarding executive functions: Bearden, et al., [21], evaluation of executive functions via the Delis-Kaplan Executive Function System test, while other studies find poorer performance in patients with bipolar disorder and comorbidity ADHD only in those without ADHD comorbidity: Pavuluri, et al., [26], after evaluation of executive functions via different tests, the Cogtest Set Shifting, the Penn Conditional Exclusion Test, Controlled Oral Word Association Test and the TMT. Thus, the likelihood of additional cognitive burden attributed to ADHD comorbidity remains controversial. Knowing that comorbid anxiety in bipolar disorder is associated with a comorbid alcohol use disorder [27] and that there appears to be a continuum between bipolar disorder and ADHD diagnoses, it could there is a common third factor or vulnerability factors common to these disorders that complicate the assessment of cognitive dysfunction attributable to each.

Repercussions of cognitive disturbances on the quality of life

The question was what was the impact of cognitive impairment on the quality of life of patients with bipolar disorder in order to assess the value of making cognitive deficit a therapeutic target. It was also necessary to ask the question of the variables associated with the psycho-social functioning of these patients. It was wondered whether the psychosocial functioning was more disturbed by cognitive disorders or mood symptoms, the two not being totally independent [28,29]. A significant association was found between psychosocial functioning and clinical status (scores on the Hamilton Depression and Young Manic scales) and between psychosocial

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functioning and verbal memory (CVLT). However, psychosocial functioning was found to be more correlated with cognitive variables than with clinical variables [28]: Poor psychosocial functioning was associated with poorer performance in the backward digit span and total CVLT cognitive variables, both during thymic episodes and in euthymia, when it was only associated with the total number of thymic episodes among the clinical variables evaluated. The authors assessed the functioning of patients via the Global Assessment of Functioning Scale (GAF) but also by assigning to patients who have no professional activity or poor occupational activities in the last three years prior to the evaluation, the qualification " poor functioning ". In agreement with GAF, well-functioning patients performed significantly better in tasks involving learning and verbal memory (at all measures in the CVLT, p was less than or equal to 0.005).

In 2009, Wingo, et al., conducted a review of the literature on the functional impact of cognitive disturbances in bipolar disorders [30]. In 11 of the 13 studies selected by the authors, there was a significant association between impairment of cognitive function and impairment of psychosocial functioning after adjustment for residual mood symptoms, other clinical variables, and demographic variables. The authors regretted the absence of an objective measure of functional status that sometimes seemed to result from a subjective assessment (two studies were based on a self-evaluation of patients at functional scales) or was sometimes not explained at all (three studies claimed to have simply assessed the social and occupational functioning without specifying the means used for this evaluation). The rest of the studies retained by the authors used variable scales: the GAF (7/13 studies), the Impairment Rating Scale (IRS), the Structured and Scale Interview of Maladjustment (SSIM), the Social Adjustment Scale (SAS), the Multidimensional Scale for Independent Living (MSIL) and the Instrumental Activities of Daily Living (IADL). The functional areas assessed ranged from general autonomy to quality of interpersonal relationships, to recreation and home maintenance. In studies assessing psychosocial functioning in euthymic patients, the average GAF scores were 19% higher than the average found in controls. Specifically, 55% of people with bipolar disorder would be unemployed, in another paper, it was found a significant association between use and cognitive functioning in bipolar disorder [31]. Huxley, et al., cite figures of over 19% (19%-58%) of homeless individuals and less than 25% (19%-23%) of married subjects. The functional domains may be representative of the patient's current performance: Wingo, et al., give example of a patient with bipolar disorder with residual depressive symptoms having the cognitive ability to pay his bills but lack of motivation to perform this task. There is a need to separate each variable influencing the overall functioning of the patient and more advances such as the IADL that assess basic activities of daily living. Huxley, et al., Listed 12 variables found throughout the literature to be associated or predictive of impaired functional status in subjects with bipolar disorder: male sex, altered premorbid functioning, early diagnosis of disorder, increased number hospitalizations, long recent hospitalizations, significant depressive morbidity, psychotic substance-related disorder, poor socioeconomic status, low quality social support, being single, not living in independent housing.

According to Bauer, et al., among the variables was found essentially the variable "depressive symptoms" as strongly associated with impaired functional status [32]. One might think that cognitive dysfunction worsens with the course of the disease but also that, conversely, the adverse evolution of the disease results in part from cognitive dysfunction. Cognitive functioning is thus a mediator between the evolutionary process of the disease and daily socio-occupational functioning. The overall functioning of patients in bipolar disorder appears strongly impacted. Only one third of patients would recover their level of premorbid socio-occupational functioning [31]. Thus, cognitive dysfunction appears to be one of the major causes of disability in bipolar disorder, and would be an essential lever on which to act to target functional, and not just clinical, remission of the patient. On the other hand, in animals, acute and chronic administration of vortioxetine improves performance on objective measures that cover a broad range of cognitive domains. In human, vortioxetine appears to be a useful treatment option in MDD patients with cognitive dysfunction, but it is difficult to extrapolated to bipolar patients without specific studies [33].

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Citation: Bourin M (2019) Cognitive impact in bipolar disorder. Arch Depress Anxiety 5(2): 052-058. DOI: https://dx.doi.org/10.17352/2455-5460.000042