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Cognitive impairment and dementia in bipolar disorder

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1. ABSTRACT

In bipolar disorder (BD), impaired cognition has long been described as a psychopathological feature of abnormal mood states, or accepted as treatment related side-effects. More recently, neuropsychological studies conducted in older adults have led to the recognition that enduring, irreversible cognitive changes do occur in substantial proportion of euthymic patients with life-long BD, relevant enough to warrant the diagnosis of dementia. The increased risk for dementia in BD has been associated with older age and also with factors related to the clinical course of the disease. However, it is yet to be determined whether cognitive impairment and dementia represent a complication of the most severe cases, exacerbated by biological treatments and deprivations accumulated over years, or if should be viewed as part of the natural history of BD. In the present review, we revisit the epidemiological evidence of the association between BD and dementia, and discuss the putative mechanisms supporting this association. We hypothesize that dementia may be considered as a long-term feature of BD, which is exacerbated in the presence of other risk factors.

2. INTRODUCTION

Many psychiatric disorders present with cognitive impairment as a feature of acute abnormal mental states, or with cognitive decline and dementia in the long-term outcome. In schizophrenia, for instance, cognitive impairment has been reputed as part of the natural history of the disease since early definitions of dementia praecox; more recently, correlates of hypofrontality in schizophrenic patients have been extensively investigated with the aid of neuroimaging and cognitive assessment methods (1).

Cognitive impairment is a common feature in BD. Several studies conducted in samples of young and middle-age adults have indicated that cognitive deficits largely occur during major affective episodes (both depression and mania), but can also be depicted in euthymic patients (2-6). Deficits have been described affecting verbal memory (7), executive function (7-9), attention, visual memory, mental speed (3,6,10,11) and, to a lesser extent, language (12) and visuospatial function (13). In general, the most frequently reported impairments involve executive function and verbal memory, which seem to occur regardless of age (5, 14).

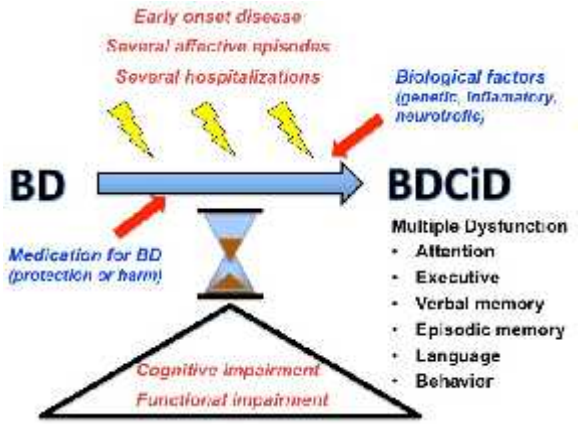

Figure 1. Multiple variables involved in the complex pathway of cognitive impairment and dementia associated with BD. Note.BDCiD=bipolar disorder cognitive impairment and dementia.

Deficits in attention, visual memory and processing speed are also very prevalent among BD patients (3, 5, 6, 10, 14). These deficits are not usually severe in non-demented BD patients, ranging between 0.2 to 1.0 standard-deviations below the respective norms (7, 14). Nevertheless, cognitive impairment negatively affects the functional capacity of patients with BD, and exerts a negative effect on the global prognosis (15).

There is undoubtedly a growing interest of clinical scientist on the cognitive burden of BD, and the number of publications in this field has increased considerably; however, methodological differences across different studies may preclude the generalization of findings and hamper meta-analytical approaches. Major limitations are the inclusion of patients in different mood states and distinct degrees of severity, the heterogeneity of treatment approaches – most of which are associated with cognitive side-effects – and differences in neuropsychological assessment methods. These limitations may lead to significant variations in effect sizes relative to one given cognitive function when assessed by meta-analysis (5, 14). Anyhow, with respect to the nature of cognitive impairment in adult patients with BD, the largest effect sizes observed by two meta-analyses indicated that executive function and verbal memory are the most frequently impaired cognitive abilities in BD (5, 14).

It is well accepted that pharmacological treatments for BD may be associated with cognitive toxicity. Most established treatments for BD, namely lithium, anticonvulsants, antipsychotics, antidepressants and benzodiazepines – not to mention electroconvulsive therapy (ECT) – may impair cognition at varying degrees and through different potential mechanisms, as a side effect or direct drug effect. However, these do not fully explain the complex pattern of cognitive dysfunction in BD and its exacerbation over time, rendering this simplistic causation at least controversial (16). The array of treatment choices for BD is wide and heterogeneous, ranging from monotherapy to the combination of several drugs, with significant variations in dose regimen, and often requiring the combination of ECT. Results from clinical trials are controversial because of different patient populations, distinct mood states, comprehensiveness of neuropsychological assessment batteries, and combination of medications with cumulative cognitive effects. Deficits in verbal memory have been associated with lithium use and with poly-medication; and psychomotor slowing has been also associated both with antipsychotic drugs and lithium (17). However, these cognitive deficits are normally reversible upon discontinuation of treatment, even if continuously used for a long window of time. Therefore, other mechanisms must be taken into account to better explain the cognitive syndrome associated with BD (Figure 1).

3. COGNITIVE FINDINGS IN LATE-LIFE BIPOLAR DISORDER

Cognition seems to be similarly impaired in BD across the life span, and geriatric BD patients also show a similar pattern of widespread cognitive dysfunction (2). In several studies, the severity of cognitive deficits was shown to increases along with the duration of illness. The earlier the onset of the disease and the older the patients' age, the higher the probability of detecting cognitive deficits in BD. Therefore, one would expect more pronounced deficits in elderly patients with longstanding BD. Cognitive deficits in elderly BD patients also appear to be different from those found in older schizophrenics. Depp *et al.* (2007) assessed clinically stable middle-aged and elderly outpatients with BD and schizophrenia, as compared to healthy controls (15). The performance of BD patients on neuropsychological tests was significantly different from normal controls, and had a distinct pattern from schizophrenics; cognitive deficits in BD were associated with poor quality of life, but not with the severity of psychiatric symptom or duration of illness (15).

Unfortunately, there are still a small number of studies addressing the cognitive findings in late-life BD. Gildengers *et al.* (2004) examined euthymic BD patients aged 60 years or more paired for age and education with healthy controls, with an assortment of cognitive tests (MMSE, the Mattis Dementia Rating Scale, and the Executive Interview), and found that half of the subjects scored one or more standard deviations below the expected norms on these tests (18). From the available studies in older populations, it seems that elderly subjects with BD may have a similar pattern of cognitive impairment when compared to younger patients (see Table 1) (6; 12, 13, 15, 19, 20), although it is unarguable that older BD patients are at a higher risk for dementia in the long-term (19-22). Young *et al.* (2006) conducted a meta-analytical study addressing cognitive function in older adults with BD in a relatively small cumulative sample of 231 subjects (2). The authors faced the limitation that the majority of subjects were either in depressed or manic states, and the set of cognitive data was based on basic cognitive screening test such as the MMSE; in this study, no association was found between the age of onset of BD and the degree of cognitive impairment (2). Deficits in verbal memory, executive function and attention were frequent, similarly to the cognitive findings in younger samples (2).

Despite the importance of documenting the degree and pattern of cognitive impairment in the elderly, few studies have examined older BD patients using standardized cognitive screening methods. The available evidence is largely based from the performance on cognitive screening tests, such as the Mini-Mental State Examination (MMSE), the Clock Drawing Test (CDT) and the Verbal Fluency Test (VFT) (3, 6, 7, 12, 13, 18, 19, 23). It is important to note that these tests have been validated for the screening for dementia, with limited sensitivity to detect subtle deficits. Few studies compared the cognitive performance of patients with BD to that of patients with conditions that primarily affect cognition, such as AD (3, 6, 7, 9, 12, 13, 18, 7, 23).

In one of the few studies using cognitive screening tests in late-life BD, namely the MMSE, the CDT and the Cognitive Abilities Screening Instrument (CASI), 42.3% of patients had a positive screening, particularly when the first manic episode had occurred before the age 40 years; however, this study lacked of a comparison group (19). In another study, older patients with type I and type II BD were compared to healthy controls matched for age, gender and education level; the authors found that BD patients had a worse performance in processing speed, working memory, episodic memory and verbal fluency, but not in executive function. Upon hierarchical regression analysis, working memory and verbal fluency were shown to be dependent on processing speed, which supports the notion that the latter function is critical to global cognitive performance in the elderly (6).

4. LONGITUDINAL STUDIES: COGNITIVE AND FUNCTIONAL STATUS

There is limited information on the long-term progression of cognitive deficits in BD patients. Evidence from a few prospective studies evaluating cognition in BD subjects indicates a heterogeneous pattern of deficits in elderly patients with BD. In a study with BD patients younger than 55 years of age, 62% of the subjects had some degree of cognitive impairment which, although heterogeneous, could explain the variability in functional outcome (11). As opposed to that, cognitively unimpaired patients tend to have a higher level of psychosocial functioning, which is consistent with the findings of an inverse association between the magnitude of cognitive impairment and functional outcome (24-26). The dementia outcome in BD is correlated with the number of major affective episodes through the clinical course of the disease (27), particularly those requiring hospitalization (13). Nevertheless, there is still limited data on the long-term cognitive profile of older adults with BD.

In a two-year longitudinal study by Mur *et al.* (2008), euthymic BD patients were evaluated after being at least three months in remission from manic or depressive exacerbations (28). As compared to healthy controls, BD patients had a worse performance (1.0 to 2.0 standard-deviations below) on measures of executive function and processing speed (28). Balanza-Martinez *et al.* (2005) conducted a three-year follow-up study comparing schizophrenic and BD patients, showing that both patient groups were more impaired in several neuropsychological measures than healthy controls (29). Although the sample size this study was relatively small, and controls were assessed only once, the authors concluded that both schizophrenics and BD patients had persistent cognitive deficits. In another three-year follow-up study, Gildengers *et al.* (2009) compared 36 subjects with BD (type I and II) to healthy controls matched for age and education (20). Participants were neuropsychologically assessed at baseline and longitudinally, taking into account that BD patients were only examined if euthymic. As compared to controls, BD patients performed significantly worse both at baseline and follow-up, presenting with a more rapid cognitive decline than expected in their age and education groups (20). Similar findings were presented by Moorhead *et al.* (2007), indicating that the overall rate of cognitive deterioration after four years of follow-up was greater in BD patients than in normal controls (30).

Tohen *et al.* (2000) demonstrated that functional impairment is a common feature of euthymic BD patients (31). In many cases it is difficult to determine whether functional impairment is a consequence of residual mood symptoms or if, in fact, is determined by cognitive deficits. The impact of cognitive dysfunction on functional and social status in adult patients with BD has been addressed by a few important studies. Three longitudinal reports indicated that cognitive deficits in BD may predict a poor psychosocial adjustment in the long-term, with verbal fluency, psychomotor speed, verbal memory, executive and attentional functions being independent predictors of functional recovery after one year (32-34). More recently, Burdick *et al.* (2010) evaluated 33 patients who were diagnosed as having type-I BD at an index hospitalization that had occurred 15 years before (35). The outcome variables included affective symptoms, cognition, functional status, engagement in work, and social adjustment. Global functional impairment was significantly associated with poor cognitive performance, particularly on a measure of processing speed; impaired social functioning was associated with a worse performance on digit symbol test (35). Neither the severity nor duration of the illness was significantly correlated to measures of global functioning. The authors suggest that processing speed is an important predictor of social and global functioning in patients with BD (35).

Younger patients with BD display functional deficits that can be settled between healthy subjects and those found in patients with schizophrenia. Unfortunately, controlled studies addressing functional status in older BD patients are scarce. Anyhow, older patients with BD, as well as older schizophrenics, tend to be more functionally impaired than age-matched individuals. Many clinical factors render BD elders more prone to such deficits, including age-associated cognitive decline, cumulative effect of recurrent affective episodes during lifetime, slower recovery from episodes, and medical comorbidities (36). In a controlled study addressing quality of life and global functioning in middle-aged and older adults with BD and schizophrenia, both patient groups had a worse quality

of life and global health status than healthy controls; however, BD patients had more medical comorbidities than schizophrenics. In addition, cognitive impairment and affective symptoms were associated with worse quality of life and lower social functioning in BD group (36). Accordingly, a small study in subjects with BD further showed that executive dysfunction and abnormal processing speed are strongly correlated with impairment in instrumental activities of daily living (3). A recent study by O'Shea *et al*. (2010) compared the performance of 29 euthymic BD patients and 29 matched controls on cognitive tests and functional measures, in order to determine the association between cognitive impairment and social and occupational function (23). Patients with BD had a worse performance on ecologically valid tests of attention, memory and executive function, in addition to general, social and occupational functioning. Impaired cognitive function was not associated with residual mood symptoms or functioning in this study (23).

5. BIPOLAR DISORDER AND DEMENTIA: EPIDEMIOLOGICAL EVIDENCE

A few cross-sectional studies of BD patients assessed whilst in the euthymic phase of the disease found that the number of previous affective episodes was an important predictor of the severity of cognitive dysfunction (37-40). This association was further explored in other important epidemiological studies. In a cohort study conducted in Denmark, the dementia outcome was investigated in a large sample of patients with BD or major depressive disorder (MDD) (27). Subjects discharged from their first psychiatric hospital admission due to an acute affective episode (major depression or manic state) between 1970 and 1999 were evaluated for the occurrence of dementia in the subsequent years. The Danish nationwide register was used to identify participant's history of psychiatric admissions and to ascertain their diagnoses at the moment of discharge. The diagnosis of dementia was based on the 8^{th}, 9^{th} and 10^{th} versions of the International Classification of Diseases (ICD), without specification of the etiology of the dementing disorder (27, 41). The association between the number of previous hospital admissions due to abnormal mood states and the subsequent diagnosis of dementia was estimated using a Cox proportional hazards regression model in a sample of 18,725 patients with MDD and 4,248 with BD. The authors reported an overall trend towards increased the risk of dementia in patients diagnosed as with BD and MDD, and a positive correlation between the number of episodes requiring hospitalization and the occurrence of dementia. This association was stronger among patients with MDD than BD; on average, each additional episode increased the rate of dementia diagnosis by 13% for MDD and by 6% for BD. BD patients who had multiple (five or more) acute episodes had a significantly higher risk of dementia as compared to those who had a single episode (hazard ratio 3.19, 95% CI 0.69 to 14.75) (27).

In a cross-sectional study conducted in our group addressing the occurrence of cognitive impairment in a sample of euthymic older adults with BD, the diagnosis of dementia was established in 19% of the subjects (21). This estimate was almost three times higher than the prevalence of dementia observed in an age-matched population (21). In this particular study, 118 patients with BD underwent extensive cognitive and functional assessment. Patients were classified, as having normal cognitive function, mild cognitive impairment and dementia; laboratory and imaging methods were used to further decide upon a presumably vascular or primary degenerative etiology in the latter cases. In other words, demented BD patients were submitted to the diagnostic criteria for vascular dementia, Alzheimer's disease (AD), mixed-type, or dementia due to other causes. AD was found to be the most frequent classification of demented patients in this sample. In addition, subjects were divided in two groups according to the previous history of treatment, i.e., long-term lithium or treatment with other mood stabilizing drugs. Patients treated with lithium had a statistically significantly lower prevalence (5%) as compared patients treated with other drugs (33%). In addition, demented patients had a higher duration of BD and a higher number of previous depressive episodes (21).

In an observational cohort study, Kessing and collaborators (2008) further evaluated the association between the chronic use of lithium and the risk of dementia (22). The authors analyzed registers of 16,238 subjects who had purchased lithium salts in Denmark between January 1995 and December 2005. The underlying hypothesis was that being prescribed lithium chronically (presumably for the treatment of mood disorders) might lower the prevalence of dementia. The comparison group was composed by a random sample of 1,487,177 individuals (30% of the general local population) who had never received such prescription. Individuals who purchased lithium only once had an increased rate of dementia (relative risk 1.47; 95% confidence interval 1.22-1.76), and those purchased lithium two or more times had a prevalence of dementia within the same range of that observed in the general population (22). No such association was found for the prescription of anticonvulsants. It is reasonable to think that individuals who purchase lithium salts only once according to the first prescription (each one usually holding 100 tablets), but do not continue any further, may represent patients with affective disorders (mostly BD) who either discontinued treatment or did not tolerate lithium salts, being therefore switched to other medications. As opposed to that, chronic lithium users (presumably BD patients) were able to benefit from the putative neuroprotective effect of lithium leading to a decrement in the rate of dementia. The same group in Denmark evaluated patients diagnosed with mania or BD who had been discharged from a psychiatric hospitalization (42). The study group (n=4,856) was stratified according to the prescription of lithium salts, and the subsequent diagnosis of dementia was ascertained in this sub-sample between 1995 and 2005 (42). From this sample 2,449 patients were exposed to lithium and 216 received a diagnosis of dementia during follow-up (103.6 ⁄ 10.000 person-years). Similarly as observed in the previous study, a decreased rate of dementia was observed among those who maintained lithium treatment; no such effect was

Table 1. Cognitive functions possibly impaired in late-life bipolar disorder

Sustained attention
Processing speed
Abstraction
Planning
Inhibitory control / perseveration
Working memory
Episodic memory
Verbal fluency
Verbal recall (both short and long)
Verbal learning

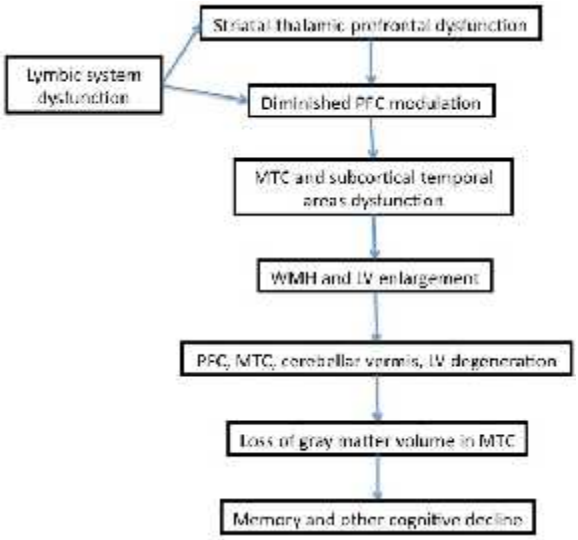

Figure 2. Hypothetical model of neuroanatomical dysfunction and degeneration leading to cognitive impairment and dementia in BD. Note. PFC=prefrontal cortex; MTC=medial temporal cortex; LV=lateral ventricule.

observed for the use of anticonvulsants, antidepressants, or antipsychotics (42). These findings reinforce the notion that chronic lithium use may be associated with neuroprotective effects, which may be delivered through the unspecific modification of neurotrophic and neurodegenerative cascades, such as up-regulation of neurotrophic factors (e.g., BDNF) (43) and autophagy (44); inhibition of apoptosis (45) and glycogen-synthase kinase signaling (46) This combined effect may yield a relative protection against dementia to BD patients undergoing chronic lithium therapy.

6. NEUROIMAGING CORRELATES OF COGNITIVE DYSFUNCTION IN BIPOLAR DISORDER

Structural and functional neuroimaging studies are complementary to the clinical evaluation of cognitive impairment in BD and its association with dementia. A neuroanatomical model of BD proposes that dysfunctional striatal-thalamic-prefrontal networks and associated limbic regions leads to a diminished prefrontal modulation of subcortical and medial temporal structures within the anterior limbic network (47). Cognitive changes both in young and elderly subjects with BD have been linked to structural brain changes that can be depicted by magnetic resonance as white-matter hyperintensities; such abnormalities have been associated with a worse outcome (48). In a meta-analytical study, only right ventricular enlargement was consistently found in BD patients (49). There is increasing evidence for medial-temporal and prefrontal abnormalities in BD (50). Prospective neuroimaging studies are essential to evaluate progressive cognitive deterioration. Some cerebral regions like the cerebellar vermis, the lateral ventricles and inferior prefrontal regions appear to degenerate with repeated major affective episodes. These structural changes may represent long-term effects of illness progression, once this was not associated with cognitive decline (47). In a longitudinal study in which BD patients and age-matched controls were reassessed after four years, Moorhead *et al.* (2007) found that reduction in memory function and loss of gray matter volume in medial temporal cortex were correlated with the severity of the disease (30). Although this evidence does not warrant a cause-effect relationship, this is the strongest evidence to date in favor of a direct correlation between the clinical course of the illness, abnormal cognition and neuroanatomic changes. Figure 2 illustrates a hypothetical model for a correlation between cognitive degeneration in late-life BD and neuroanatomical structures dysfunction.

7. CONCLUSIONS AND FUTURE DIRECTIONS

Although more common during major affective episodes (2, 4, 51), cognitive impairment may be persistent and detectable in euthymic and non-medicated BD patients. This suggests that cognitive impairment may in fact regarded both as a state and a trait of BD, representing therefore two distinct endophenotypes of the disease. The cognitive impairment that occurs during acute manic and depressive states tend to be benign and reversible, and are probably related to abnormal functional states; conversely, BD also presents with persistent and progressive impairments that are presumably subsequent to the long-term burden of the disease, and associated with intracerebral pathology (3, 5, 6, 14, 19, 52). The study of incident cognitive deficits in older adults with BD, in association with neuroimaging and other biological markers, may shed light into this important question.

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