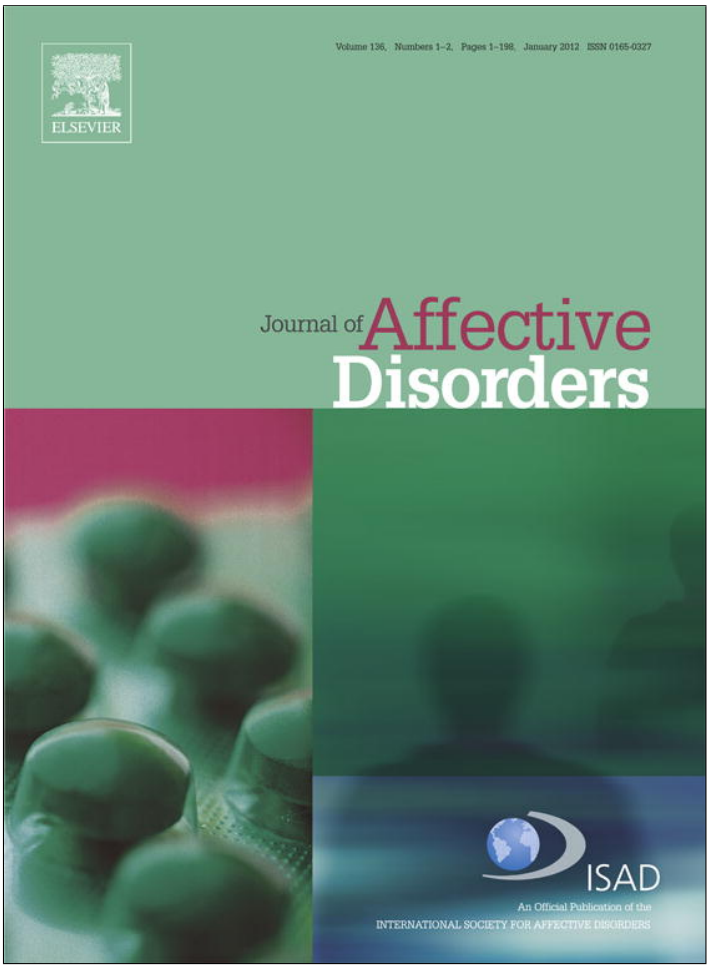

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Special review article

The trajectory of neuropsychological dysfunctions in bipolar disorders: A critical examination of a hypothesis

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ABSTRACT

Objective: The hypothesis of a progressive nature of neuropsychological deficits in bipolar disorders is often accepted as an axiom by many clinicians and researchers in the field. However, contradictory pieces of data and a number of methodological concerns put it under debate.
Method: We reviewed findings from three different approaches to the study of the trajectory of cognitive features in bipolar disorders: longitudinal evaluation of cognition in affected subjects, cross-sectional neuropsychological assessment of patients belonging to different age groups, and exploration of the risk of dementia in bipolar subjects.
Results: An increased risk of developing dementia was found in bipolar subjects. However, evidence from cross-sectional studies did not show more severe cognitive deficits in patients with longer illness duration. Furthermore, longitudinal studies revealed that bipolar subjects' cognitive performance did not change between different points in time.
Conclusions: After a thorough discussion of these findings and the limitations of the different approaches, we argue that, at present, there is no consistent evidence supporting that bipolar disorders, as a group, have a progressively deteriorating course of cognitive functions. Furthermore, we highlight the possible influence of psychotropic agents and metabolic factors on neuropsychological outcomes. Finally, we discuss the clinical implications of these findings and propose targets for forthcoming research.

Contents

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1. Introduction

Despite having observed that some patients affected by manic-depressive insanity (MDI) could suffer a deteriorating course, Kraepelin (1899, 1919) developed his classification of psychoses on the basis of the contrast between the deterioration of cognition and behavioral capacities of dementia praecox and the relative indemnity of the course of MDI. During most of the twentieth century, especially after pharmacotherapy reached the psychiatric field, this way to conceptualize the course of MDI became even more extreme. The fact that a significant number of people with psychotic or atypical forms of bipolar disorders (BDs) were misdiagnosed as schizophrenics helped to increase this contrast (Pope and Lipinski, 1978). By the end of that century, BDs were regarded as relatively benign illnesses in which patients' intellect and cognitive abilities were preserved and as easily treatable "*with some lithium*".

At the beginning of the twenty-first century, BDs regained a place of interest in the psychiatric field, and it did not take long for psychiatrists to understand that a misconception about these disorders had been held. From then on, increasing amounts of data have revealed that only less than a half of patients exhibit preserved neuropsychological functioning, whereas the remaining percentage of affected people suffer significant cognitive deficits, even in euthymia (Gualtieri and Morgan, 2008; Iverson et al., 2011; Burdick et al., 2014; Martino et al., 2014). Hence, this has been the moment of the debunking of the notion of cognitive indemnity of BDs. In the last decade, research on neuropsychological aspects of BDs has experienced an exponential growth, and cognitive dysfunction has been shown to be one of the strongest predictors of functional recovery (Tabarés-Seisdedos et al., 2008; Martino et al., 2009; Bonnín et al., 2010). Hence, cognitive features are currently acknowledged as an important piece of the clinical description of BDs. However, in the last few years, this conceptual revolution has become even more profound. A series of data and hypotheses are proposing that cognitive dysfunctions may progress along the course of the disorder. These proposals were initially supported by evidence of a negative association between the number of episodes, especially manic ones, and neurocognitive functioning (for a review see Robinson and Ferrier (2006). Further studies corroborated that patients with the first manic episode displayed better cognitive outcomes than patients with multiple episodes (López-Jaramillo et al., 2010). Another recent review summarized the positive evidence that cognitive impairments increase as a function of the number of prior episodes in patients with BD (Post et al., 2012). Moreover, this association is now usually referred to as further evidence of illness progression and staging in BD (Berk, 2009; Kapczinski et al., 2009, 2014; Post et al., 2012). Specifically, staging models suggest a progression from early stages, in which no cognitive impairments are evident, to late stages of illness, in which cognitive impairments prevent patients from living independently (Kapczinski et al., 2009).

At present, the hypothesis of a progressive course of cognitive deficits in BDs is being received with great interest. However, it is often presented as a self-evident truth rather than as a hypothesis subject to test. It is noteworthy that all these data about the relationship between the number of prior episodes and cognition are based exclusively on cross-sectional studies and, thus, the direction of causality cannot be established. In fact, in a recent study by our group, no evidence was found to support the hypothesis of a progressive course of cognitive impairments as a result of the number of previous episodes, and alternative ways of interpreting the above-mentioned relationship were proposed (Martino et al., 2013b). Therefore, further evidence is needed before concluding that cognitive impairments are progressive in BDs.

Accordingly, the aim of this narrative review was to summarize and put into perspective the evidence gathered in recent years that could contribute to our knowledge about the longitudinal trajectories of cognitive functioning in BDs. Taking into account that accepting a progressive course of cognitive dysfunctions in BDs may have important implications in the way in which clinicians, researchers, health authorities, and affected people conceptualize the prognosis of these disorders, a discussion from a clinical point of view was included.

2. Material and methods

In order to gain evidence about longitudinal trajectories of cognitive functioning in BDs, we reviewed three data sources: 1) Longitudinal follow-up studies of neurocognitive functioning in patients with BD. This approach enables to directly explore the longitudinal course of cognition in affected subjects. Under the hypothesis of a progressive course of neuropsychological deficits, we should expect a worsening of cognitive outcomes over successive neuropsychological evaluations; 2) Comparison of cross-sectional neurocognitive studies of euthymic patients along different stages of life such as pediatric, young adult, and elderly bipolar subjects. By means of this indirect approach we can gain insight into the evolution of neuropsychological features, as it could be hypothesized that the extent and/or magnitude of cognitive deficits would be larger in older age if deficits were progressive; and 3) Studies assessing the association between BD and a subsequent diagnosis of dementia. Similarly to the above-mentioned approach, it may be hypothesized that patients with BD would have an increased risk of developing dementia if cognitive impairments were progressive.

With this structure in mind, we performed an extensive computerized literature search of articles published in English in the last three decades. Special consideration was given to results from meta-analyses, when available, as they provide more precise estimates of effect magnitude than data derived from primary studies. Data resulting from our search were presented in an exhaustive fashion, regardless of whether they support the hypothesis of a progressive pattern of cognitive dysfunctions or not.

3. Results

3.1. Longitudinal studies of cognitive function in BDs

Longitudinal research is clearly the best approach to gaining insight into longitudinal trajectories of neurocognitive functioning. A recent meta-analysis (Samamé et al., 2014) summarizing the results of longitudinal studies of euthymic adult patients did not show any significant differences between BD patients' performance at baseline and after a mean follow-up period of 4.62 years for 14 cognitive variables. Unfortunately, data from controls were scant and only made it possible to perform meta-analyses for four cognitive variables, for which no patient–control differences were found regarding test–retest effect sizes including a mean interval of 2.22 years. Furthermore, four out of the 12 articles included in the study were based on elderly patients (Depp et al., 2008; Delaloye et al., 2011; Schouws et al., 2012; Gildengers et al., 2013), who have been proposed to display a more pronounced age-related cognitive decline over time than healthy controls (Gildengers et al., 2004). However, at the primary study level neither of these reports showed patient–control differences regarding long-term cognitive functioning, not even when late-onset patients were included.

Among recently released studies, Torres et al. (2014) analyzed the one-year trajectory of cognitive deficits in recently diagnosed bipolar patients and reported an improvement over time in BDs for processing speed and executive function relative to the control group. In accordance, Santos et al. (2014) analyzed the five-year course of cognitive functioning in a large sample of bipolar patients and showed that the trajectory of cognitive deficits did not differ from that of healthy controls.

Do available longitudinal studies support the notion of a progressive pattern of cognitive dysfunctions? Taken together, these pieces of evidence do not support the notion that cognitive deficits worsen with illness duration. However, for the purposes of this discussion, some methodological limitations should be considered. The follow-up periods utilized may have not been long enough to capture any possible changes in cognitive functioning. Furthermore, there was a lack of control for confounds such as mood variations and medication status. Possible drop-out bias is another weakness of longitudinal studies, but some reports comparing patients who completed the whole study with those who dropped out did not find any significant differences (Torrent et al., 2012; Braw et al., 2013; Gildengers et al., 2013).

3.2. Cross-sectional studies of cognition in pediatric, young adult, and elderly euthymic bipolar patients

The neuropsychological assessment of bipolar subjects belonging to different age groups indirectly sheds light on the course of cognition in BDs. If cognitive deficits worsen with illness duration, then we should expect cognitive performance to be more severly impaired in elderly patients. Meta-analyses of euthymic young adult patients (Robinson et al., 2006; Torres et al., 2007, Arts et al., 2008; Bora et al., 2009; Kurtz and Gerraty, 2009; Mann-Wrobel et al., 2011) have consistently reported moderate ($0.5 < d < 0.8$) and large ($d \geq 0.8$) deficits across executive processes, verbal memory, attention, and processing speed. With regard to pediatric bipolar subjects, two meta-analyses (Joseph et al., 2008; García Nieto and Castellanos, 2011) have shown moderate deficits ($0.5 < d < 0.8$) for verbal memory, attention, processing speed, and executive domains. However, they were based on primary studies of patients in different phases of BD. Data on euthymic patients during childhood are very scant so far. The largest study of cognitive performance in euthymic pediatric patients found large impairments ($d \geq 0.8$) for executive domains, verbal memory, and attention in a sample of 28 children, out of which 14 had comorbidity with ADHD (Pavuluri et al., 2006).

Finally, although evidence from old adults with BD is currently quite limited, a recent meta-analysis of neurocognition in late-life BDs (Samamé et al., 2013) revealed moderate impairments for the cognitive variables analyzed, except for phonemic fluency ($d=0.80$) and cognitive flexibility ($d=0.88$). In order to analyze a more homogeneous sample mostly composed by early-onset patients, and thus gain further insight into long-standing BD, the results derived from late-onset bipolar subjects were removed, when possible, from meta-analyses, and overall effect sizes were recalculated. The summary estimates became much smaller, with cognitive flexibility barely reaching the large range ($d=0.83$) and patient–control differences for serial learning becoming non-significant.

Looking at these data from a temporal perspective, it is not possible to infer an effect of time on cognitive function in BDs, given that the extension and magnitude of cognitive dysfunctions found in young adult and elderly patients are very similar. So as to provide an example, the overall effect sizes yielded by meta-analyses of cognition in euthymic young adult and elderly BD subjects are summarized (Table 1). In accordance with these findings, the only study comparing neurocognitive performance between euthymic young adult and elderly BD patients on different neurocognitive tasks yielded no significant differences (Strejilevich and Martino, 2013).

Do cross-sectional studies of cognition in pediatric, young adult and elderly euthymic bipolar patients support a pattern of progressive course of cognitive dysfunctions? Data from neuropsychological research on bipolar patients in different stages of their lifespan do not indicate an association between late-life BDs and more pronounced cognitive impairment, and therefore do not support the hypothesis of a progressive nature of cognitive deficits in BDs. The main limitation of the above-described approaches is that almost all studies of cognition in bipolar elders excluded subjects with dementia, and it is also possible to speculate that subjects with a worse course of illness have a shorter life expectancy and are therefore under-represented in samples of elderly patients.

3.3. Risk of dementia in BD subjects

One of the most referenced arguments in support of the hypothesis of neuroprogression is the evidence of an increment in the risk of suffering dementia in subjects with affective disorders (da Silva et al., 2013). Some small pioneering studies of non-euthymic bipolar elders found that a high percentage of them scored positively on screening tests for dementia (Dhingra and Rabins, 1991; Gildengers et al., 2004). In an analysis of the Danish Psychiatric Case Register of Admissions, Kessing et al. (1999) calculated the rates of discharge diagnosis of dementia among people who had been previously discharged with the diagnosis of BD, unipolar depression, schizophrenia, and neurosis along 21 years of follow-up and compared them with the rates of admission to psychiatric hospitals with a discharge diagnosis of dementia for the total Danish population. The results indicated that subjects with BD had the highest risk compared to the general population and the other psychiatric diagnoses. In a second report, Kessing

Table 1
Results of meta-analytic studies of neurocognitive functioning in young adult (Robinson et al., 2006) and elderly bipolar patients (Samamé et al., 2013).

Cognitive variables	No. of studies		BD		HC		Effect size		95% CI	
	Adult	Elderly	Adult	Elderly	Adult	Elderly	Adult	Elderly	Adult	Elderly
Sustained attention	7	5	191	197	186	171	0.60	0.61	0.38–0.82	0.39–0.82
Serial learning	10	3	344	192	347	131	0.90	0.76	0.74–1.06	0.02–1.49
Delayed recall	10	5	345	228	349	187	0.73	0.71	0.57–0.89	0.33–1.08
Forwards digit span	5	3	222	181	209	120	0.47	0.61	0.28–0.66	0.38–0.85
Backwards digit span	5	3	222	181	209	120	0.98	0.77	0.33–1.63	0.53–1.01
Semantic fluency	4	5	149	234	135	193	1.09	0.75	0.84–1.35	0.55–0.95
Phonemic fluency	8	4	235	201	228	160	0.34	0.80	0.15–0.52	0.43–1.16
TMT-B	12	3	418	161	355	140	0.78	0.88	0.42–1.14	0.64–1.12

BD=bipolar disorder patients; HC=healthy controls; CI=confidence interval;TMT-B=Trail Making Test, part B.

and Nilsson (2003) compared the diagnosis rate of dementia among BD patients with that of people diagnosed with osteoarthritis and diabetes and found that the diagnosis of BD still determined the highest risk. Interestingly, in another analysis they explored the impact of the number of psychiatric admissions on the risk of suffering dementia and found no statistically significant results (Kessing and Andersen, 2004). In accordance, a recent study by Wu et al. (2013) including 9304 patients from Taiwan's National Health Insurance (NHI) Research Database revealed, after statistical control for covariates (middle-age diagnosis of cerebrovascular disease, diabetes, dyslipidemia, hypertension, alcohol–substance related disorders, and health service utilization), that the diagnosis of BD was significantly associated with an increased odds of dementia [adjusted odds ratio=4.07 (3.08–5.37)].

Nevertheless, some limitations must be taken into account to interpret the results of these investigations. In the studies by Kessing et al., only those patients who had at least one psychiatric admission were included, with the consequence of having over-represented the most severe cases in their sample. In the study by Wu et al., the percentage of BD subjects was strikingly low, despite the reported prevalence rate (0.25%) being similar to that of bipolar patients treated in the Taiwan NHI. Second, the diagnoses were not made systematically and for the purposes of these studies. Hence, we cannot rule out possible diagnostic errors, such as confusing some presentations of bipolar episodes with dementia syndromes, a previously reported situation (Velakoulis et al., 2009). Third, early and late-onset patients were analyzed together. Epidemiological studies have proposed age at illness onset as a subtype marker of BDs (Leboyer et al., 2005), identifying a late-onset subgroup (LOBD), which would represent 21% of patients (Bellivier et al., 2003). LOBD patients have more neurological comorbidities, including early presentations of dementia syndromes (Azorin et al., 2012; Shulman and Post, 1980), and display more severe cognitive impairments than those developing BD early in their life, despite receiving shorter exposure to variables that might impact negatively on cognition (Schouws et al., 2009; Martino et al., 2013a). Although Wu and colleagues excluded those patients diagnosed with BD less than five years before the diagnosis of dementia, the problem was not entirely solved, because the mean age of the subjects included in this study was 74 ± 8.6 years, but the cut-off to be considered as belonging to the late-onset subgroup is 39.2 ± 9.6 years (Bellivier et al., 2003).

Does the increased risk of dementia support the hypothesis of a progressive pattern of cognitive deficits in BDs? Leaving aside the discussed limitations, current data support the idea that people suffering from BDs have a higher risk of developing dementia. However, this would not be an adequate argument in support of a progressive model of cognitive evolution. First, the acceptance of these data would imply that only 6–9% of BD patients suffer a dementia outcome (Kessing et al., 1999), whereas more than 90% of them would not. So, dementia would be an infrequent malignant form of evolution rather than the rule. More important, these studies have not shown the mechanism by which the increases in the risk of suffering dementia occur. The presence of dementia in BD subjects is not necessarily a consequence of the progressive worsening of cognitive deficits related to BD itself. Rather, many other factors may be related to this outcome. For example, in some patients, cognitive dysfunctions in middle age might reduce cognitive reserve, increasing the vulnerability to other factors which can increase the risk of dementia (Meng and D'Arcy, 2012). Furthermore, the interaction between obesity–cardiovascular risk factors and cognitive deficits-dementia has been proved in non-psychiatric (Farr et al., 2008; Naderali et al., 2009) and psychiatric patients (Lindenmayer et al., 2012) and the links between obesity–cardiovascular risk factors and dementia–BDs are so strong and complex that it is not yet possible to elucidate the causal direction of this relationship in light of the available data. Finally, BD subjects could co-inherit some risk factors for dementia, similarly to what has been described for autoimmune thyroiditis and BDs (Vonk et al., 2007).

4. Discussion

As an overall result of this review we can conclude that the evidence available at present does not support the notion of a progressive decline of cognition in BD patients, as a whole, due to illness evolution. None of the pathways explored in this review support this hypothesis. First, although current data are clearly insufficient to adequately answer whether cognitive deficits in BD are static or progressive, it should be noted that the available follow-up studies did not find a time effect on the course of cognitive dysfunctions, not even those based on elderly patients. Second, the analysis of cross-sectional evidence reveals that the differences between patients and healthy controls regarding cognition do not vary according to the age of the evaluated subjects. This reflects, in an indirect way, that the natural course of BDs throughout the lifespan may not have an effect – positive or negative – on cognitive deficits. Finally, although a higher risk of suffering dementia would be present among bipolar patients, this is not reason enough for inferring a progressive pattern of cognitive deficits in these disorders. Therefore, it is necessary to accept that the idea of a progressive detrimental effect of episodes on BD patients' cognitive outcomes remains as a hypothesis that needs to be tested.

However, although currently available data do not support the hypothesis of a progressive course of cognitive deficits in BD, they do not allow for the establishment of a model of evolution of these neuropsychological features. Some critical problems should be addressed before proposing an appropriate model. First, it is evident that direct and indirect effects of psychopharmacological treatment on cognition should be more extensively and deeply explored. A series of data have demonstrated that, in bipolar patients, exposure to antipsychotics is positively correlated with executive dysfunctions regardless of whether subjects suffered psychotic symptoms or not (Donaldson et al., 2003; Frangou et al., 2005; Torrent et al., 2011). A post-hoc analysis of a longitudinal study of subjects with a recent resolution of their first manic episode revealed that those patients discontinuating antipsychotic treatment had greater improvement in cognitive function (Torres et al., 2014). These data are in keeping with similar findings from healthy volunteers and schizophrenic patients (Faber et al., 2012). We have found an example of this issue in recently published research. Gildengers et al. (2014), by means of a cross-sectional design, noted that the total gray matter volume of 54 elderly bipolar I patients was independently related to lifetime duration of the disorder ($R^2=0.20$), thus providing new data in support of a neuroprogressive model of BDs evolution. However, exposure to antipsychotics and risk/burden of cerebrovascular accident were also significant and independent predictors of gray matter volume but with a larger effect –the double– than chronicity ($R^2=0.38$ and 0.44 respectively).

Conversely, convergent data from observational, prospective, and randomized studies have shown that exposure to lithium could decrease the risk of developing dementia in bipolar patients (Mauer et al., 2014). Moreover, this effect was observed by Kessing et al. (2008) in the same database previously used to investigate the risk of dementia. In the same line, and with clear relationships with pharmacological treatment, endocrinal, metabolic and cardiovascular issues can modulate cognitive evolution. Two recent studies have found a positive correlation between obesity–metabolic syndrome and cognitive impairments in BDs (Yim et al., 2012; Depp et al., 2014). Such correlation could be even greater than in schizophrenia and

may present a magnitude similar to that usually found between euthymic bipolar patients and normal controls (Depp et al., 2014). BD patients have close than double risk of developing obesity, diabetes, hypertension, and vascular disease (Goldstein et al., 2009; McElroy and Keck, 2014). Finally, imbalances in the thyroid axis, even at the subclinical level, could modify cognitive performance (Martino and Strejilevich, 2015).

On the other hand, it has been shown that BDs are heterogeneous with respect to their cognitive features, and about 40% of affected subjects do not exhibit measurable cognitive deficits in euthymia (Martino et al., 2008; Gualtieri and Morgan, 2008; Iverson et al., 2011; Martino et al., 2014). Hence, it is not possible to formulate a global description of cognitive evolution in BDs like for Alzheimer's disease or fronto-temporal dementia.

Finally, another basic question that needs to be answered before proposing a description of cognitive evolution in BDs is when and how cognitive deficits emerge. The data here reviewed do not allow for the assumption of a progressive course of cognitive deficits. However, this statement only applies to the time in which the disorder is fully established and along its course, but does not explain when and how such dysfunctions appear. The results of a recent review on cognition in the premorbid phases of BDs do not answer this question unambiguously (Martino et al., 2015). Meanwhile, it is possible to speculate with many other patterns of cognitive evolution, including the theoretical possibility of finding models of evolution in which a window of time would be present, thus making it possible to develop preventive actions in order to arrest cognitive deficits. Future research aimed at describing such potential patterns should prioritize exhaustive control of age at onset, exposure to antipsychotics and lithium, and comorbidity with vascular–metabolic disease, among other factors that could modulate cognition.

5. Conclusions

Despite the lack of consistent evidence, the hypothesis of neuroprogression has been received naturally and, perhaps, with too much enthusiasm and a lack of adequate criticism. This could be due to the fact that this hypothesis not only provides a framework for integrating basic research findings but a model of evolution for a group of disorders that still do not have a physiopathological explanation. However, it is worth remembering that, in the field of schizophrenia, the discussion of this issue has travelled a similar path, from which we can learn some lessons. About 10 years ago, the neurotoxic effects of psychotic episodes and the progressive worsening of cognitive deficits in patients with schizophrenia were accepted as a truism (Lieberman, 1999; DeLisi, 2008). Such hypothesis was reinforced by neuroimaging studies showing progressive changes in brain structure (van Haren et al., 2008; Andreasen et al., 2011). Concordantly to that, a neuroprotective effect of atypical antipsychotics was suggested. However, these assumptions are being seriously questioned today (Zipursky et al., 2013) given that follow-up studies have failed to demonstrate a progression of cognitive and functional deficits as a general pattern of evolution of schizophrenias (Szöke et al., 2008) and the fact that many of the neuro-anatomical changes initially attributed to the disorder are now starting to be considered side effects of antipsychotics (Navari and Dazzan, 2009; Moncrieff and Leo, 2010; Ho et al., 2011).

It is necessary to be aware that, at this point, we are dealing with too many inconsistencies as to adequately describe not only cognitive evolution but the overall long-term course of BDs or as to propose models able to consolidate pathophysiology, phenomenology and prognostic course (Malhi et al., 2014). Hence, we need to be doubly cautious at the time of testing and accepting models of cognitive evolution and privilege a clinical perspective to guide our decisions. Due to the direct connection between cognitive deficits and socio-vocational capacities, the way in which we conceptualize the evolution of cognition in BDs would also deeply influence the hopes and fears of affected people and the professionals involved in their care. Although the acceptance of a neurotoxic mechanism could encourage clinicians and patients to make their best attempts to avoid affective crises, it could also reduce the efforts for the patients that have already suffered many episodes, thus increasing stigma among these people. On the other hand, the assumption of models conceptualizing progressive cognitive evolution as a result of intrinsic mechanisms of the disorder could lead clinicians to attitudes of therapeutic nihilism, discouraging the exploration and management of factors already known to produce cognitive decrements in bipolar patients. For example, if we assume that cognitive decline is basically due to the neurotoxic effect of manic crises and underestimate the direct and indirect impact (due to their metabolic effect) of antipsychotics on cognition, we should logically choose to optimize the prevention of these crises by using this kind of drugs. If, on the contrary, we assume that available data do not support a detrimental effect of illness evolution on cognition but *do* support the association between exposure to antipsychotics and metabolic syndrome, our therapeutic choices should be different.

It is clear that further research is needed to cover the current information gap. In the meantime, the data presented here confront us with a number of important clinical issues that require attention and a comprehensive discussion. For example, although in schizophrenia treatment the dilemma between antipsychotics and cognition could put clinicians and patients in a dead end today, in BDs treatment, there are more options to be explored, including possible preventive actions. Only the data about a possible neuroprotective effect of lithium and the potential cognitive damage due to antipsychotic exposure, although preliminary, are solid enough as to be taken into account in our current therapeutic discussions and research orientation.

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Conflict of interest

No conflict declared.

Contributors

Dr. Sergio Strejilevich designed the article and wrote the first draft. All authors managed the literature search and contributed to the final version of the manuscript.

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