Chapter 1

# Cognition and functioning in bipolar disorder

## Introduction

Over the last two decades it has been demonstrated that bipolar patients present both cognitive dysfunctions and difficulties in psychosocial functioning beyond the episodes of the disease, even during periods of mood stability (Martínez-Arán *et al*., 2000; Goetz *et al*., 2007; Sánchez-Moreno *et al*., 2009b). Difficulties in psychosocial functioning present especially as difficulties in adequate occupational performance and social integration, and occur not only in bipolar subtype I but also in subtype II of the disease (Ruggero *et al*., 2007). In a study carried out by the National Institute of Mental Health (NIMH) in the United States in the 1970s, fewer than half of the patients admitted for bipolar disorder returned to work after discharge. At two years, one-third of the patients demonstrated difficulties in work performance, and at five years even the patients who had been compensated in the previous two years presented alterations in social functioning. Along the same lines, one study analyzing the number of work days lost per year due to physical and mental diseases reported bipolar disorder to be one of the most disabling conditions, together with neurological disorders and posttraumatic stress disorder (Gitlin *et al*., 1995). In another European study including almost 3500 patients, psychiatrists were asked about the occupational situation of the patients one year prior to a manic episode (Goetz *et al*., 2007). The results indicated that 28–68% of the patients presented some degree of occupational problems, 21% of whom were totally unable to work.

## Neurocognitive functions

Over the last few years there has been growing interest in the study of cognitive function in bipolar disorder. This interest has been translated into an increase in the number of publications specifically related to the cognitive performance of these patients during periods of euthymia, as well as studies of first-degree relatives of bipolar patients sharing the same genetic profile but not affected by the disease, and bipolar children and adolescents. Nonetheless, the number of studies remains low in comparison with other psychiatric diseases such as schizophrenia (Balanza-Martinez *et al*., 2005). It has recently become clear that there is a need to combine research efforts, integrating neuroimaging, neuropsychology, and genetic findings, in order to respond to complex questions related to vulnerability markers for bipolar disorder.

The importance of evaluating cognitive function in these patients is due to the impact that cognitive deficits may have on general functioning. For a long time it has often been considered that worse socio-occupational functioning may be the result of affective clinical or subclinical symptoms, while the effect of cognitive dysfunctions has been underestimated.

There is evidence that different cognitive areas are altered during the acute phases of the disease, especially related to tasks involving attention, memory, executive functions, and psychomotor speed, while the general intellectual level of the patients usually remains preserved, although slight changes may be observed based on the mood state of the patient. The different findings are,

on occasions, contradictory, since bipolar and unipolar depression are not always differentiated. In addition, very few studies have been performed in manic patients, because of the difficulty in evaluating these patients in this state. Neurocognition studies in bipolar disorder have different limitations, and more studies are necessary in this area to help resolve many of the functioning problems of these patients.

Below we present a short review regarding which areas or cognitive domains may be altered and which are preserved during the remission periods of the disease, with special emphasis on the deficits that persist and are free of the influence of acute symptomatology.

## Attention

Attention constitutes the basis for all the cognitive processes, since its alteration implies difficulties in psychomotor functions, learning, and memory as well as in executive functions.

With regard to *sustained attention* there is a certain consensus with respect to its alteration in acute bipolar patients. Based on stricter criteria for euthymia, studies over the past decade have observed persistent deficits in tasks of sustained attention in euthymic bipolar patients (Clark *et al*., 2002), suggesting that this type of dysfunction may be a marker of disease trait. However, there is controversy as to whether it could be strictly considered as a cognitive endophenotype, taking into account the contradictory results found in first-degree relatives of bipolar patients not affected by the disease, using a range of measures related to the Continuous Performance Test (CPT) as a reference to assess sustained attention (Arts *et al*., 2008; Bora *et al*., 2009). On the other hand, it seems clear that the deficit in sustained attention is present at disease onset, as has been detected in a sample of patients who had recently recuperated from a first manic episode (Torres *et al*., 2007), as well as in a study including a sample of bipolar patients with a disease duration of less than five years and with a maximum of two affective episodes (Kolur *et al*., 2006). Since there is practically no information on the cognitive performance of patients prior to manifestation of the disease, attention deficits supposedly become more evident over time, although they may be present at the onset of the disease.

With regard to *selective attention,* a deficit has been observed in the active periods of the disease. In some studies improvement has been described in measures of attention after the remission of clinical symptoms, suggesting that the difficulty in focusing attention may be a sensitive indicator of clinical status. Nonetheless, other studies suggest that a deficit in selective attention may be maintained in depressed patients, despite a clear clinical improvement six months after hospital discharge. In other studies undertaken in euthymic bipolar patients a deficit in selective attention was not reported. The deficits found in other measures with an attention component, such as the Trail Making Test (TMT), were attributed to alterations in working memory. More recent investigations have described attentional dysfunctions in patients with schizophrenia, and in bipolar patients as well as their first-degree relatives compared with healthy controls on performing the Stroop Color and Word Test (SCWT). In recent years a number of studies have detected a worse performance in the measurement of interference in the Stroop test in acute patients and in those in remission, which seems to be maintained in the long term (Kronhaus *et al*., 2006), even demonstrating a similar grade of involvement to that of schizophrenic patients (Balanza-Martinez *et al*., 2005). Indeed, an altered inhibitory response has been proposed as the most evident endophenotype candidate in bipolar disorder (Bora *et al*., 2009). These findings may be linked with others more recently published that demonstrate alterations in the patterns of cerebral activation in euthymic bipolar patients compared with healthy controls using functional magnetic resonance (fMR) during the Stroop test, showing reduced ventromedial prefrontal cortex activity (Kronhaus *et al*., 2006).

## Working memory

Working memory is a storage system with limited capacity that allows manipulation of information, facilitating the performance of several cognitive tasks simultaneously. Different authors consider working memory as the basic cognitive deficit in schizophrenia. Nevertheless,

investigations increasingly indicate that bipolar patients also present difficulties in tasks requiring verbal working memory (e.g., the Digit Span WAIS) as well as in other visual or spatial tests of working memory in both the acute phases of the disease and in euthymia. According to a study by Glahn and collaborators (2006) comparing schizophrenic, schizoaffective, and bipolar psychotic and non-psychotic patients, the spatial working memory distinguishes patients with psychotic symptomatology from non-psychotic patients.

## Memory

The tests most frequently used for the assessment of verbal memory in bipolar disorder are related to word lists or remembering stories.

In general, deficits of learning and memory have been associated both with the acute phase of the disease and with periods of euthymia (Martínez-Arán *et al*., 2004b; Robinson and Ferrier, 2006). Mnemonic dysfunctions may be sensitive to subtle subsyndromic fluctuations, particularly of the depressive type, which is why some studies have proposed that these difficulties are not detectable once the effect of the subclinical symptomatology has been controlled for. Nonetheless, recent studies in which the effect of the subsyndromic affective symptomatology has been controlled for have reported the presence of alterations in verbal memory as possible markers of trait or cognitive endophenotypes. The consensus on alterations in verbal memory in euthymic patients is increasingly greater (Glahn *et al*., 2004; Robinson and Ferrier, 2006; Balanza-Martinez *et al*., 2008; Bora *et al*., 2009). One study observed that depressed and hypomanic bipolar patients differ in respect of the nature of the verbal dysfunctions: whereas depressed patients present a greater difficulty in recognition tasks, hypomanic patients present more difficulties in long-term memory (Malhi *et al*., 2007).

An investigative team in Cincinnati reported that both euthymic and manic patients demonstrate difficulties in remembering information in learning tests based on word lists, such as the California Verbal Learning Test (CVLT) (Fleck *et al*., 2003); although only manic patients present difficulties in the recognition task, thereby making difficulties in information encoding more marked in these patients, euthymic bipolar patients probably present more difficulties in the retrieval of information. Bipolar patients most likely present difficulties in the organization of verbal information during the encoding process, that is, they have problems in using semantic encoding strategies. In a recent meta-analysis, moderate to large effect sizes were found in verbal memory, especially in verbal learning and in both immediate and delayed free memory (Torres *et al*., 2007). In a comparison of the neuropsychological performance of schizophrenic and bipolar patients with respect to verbal memory, the bipolar patients showed fewer dysfunctions than the schizophrenic patients (Daban *et al*., 2006c).

On the other hand, as reflected in the International Society for Bipolar Disorders–Battery for Assessment of Neurocognition (ISBD-BANC), some tests have shown greater sensitivity in detecting verbal memory dysfunctions in these patients, such as the CVLT compared with other types of tools. One of the main reasons for finding more deficits with the CVLT is that this test incorporates the use of strategies involving an executive component, which means that the subjects can semantically organize the information to better remember it. This overlapping of verbal memory and executive functions is more marked with this test than with other verbal memory tasks such as the Auditory Verbal Learning Test (AVLT) or the Rey Auditory Verbal Learning Test (RAVLT).

With regard to visual memory, in some patients this function is impaired in the acute phases of the disease, particularly in those with a previous history of psychosis or in bipolar patients evaluated during the first episode with psychotic symptoms, according to the subscale of visual memory of the Wechsler Memory Scale (WMS) or similar tasks (Albus *et al*., 1996). Among the scarce studies carried out in bipolar children and adolescents, impairments have been described in measures of visual–spatial memory that cannot be explained by the presence of affective symptomatology or comorbidity with attention-deficit hyperactivity disorder (ADHD). Again, the findings are more discrepant when referring to bipolar patients in remission. Although some studies have observed

persistent deficits in euthymic patients with the WMS and the Delayed Matching to Sample Task (DMST), it seems that most of the studies performed did not find cognitive dysfunctions in the area of visual memory; and when reported in euthymic patients, the difficulties disappear after controlling for the effect of the subdepressive symptomatology.

One of the most consistent findings is the dissociation between explicit or declarative and implicit or procedural memory. While the first is impaired in bipolar disorder, procedural memory is preserved, similar to what occurs in unipolar depression.

Some investigations have shown that relatives not affected by the disease also seem to present difficulties in learning and verbal memory, albeit to a lesser degree. These results therefore support the contention that mnemonic dysfunctions in this area constitute a trait marker of the disease. The presence of subtle deficits indicates that cognitive deficits may represent a factor of vulnerability in the development of bipolar disorder, since they may be present at the onset of the disease but may worsen with the illness course, as will be shown later.

## Executive functions

Again, there is discrepancy among the different authors with respect to the performance of bipolar patients in tasks related to executive functions. Executive dysfunction has also been observed in euthymic bipolar patients, especially in the number of persistent errors which they make in tasks such as the Wisconsin Card Sorting Test (WCST). In addition, euthymic bipolar patients correctly complete fewer categories in this same test, especially in the case of comorbid alcohol dependence (van Gorp *et al*., 1998). In relation to other frontal function tests such as the verbal fluency tasks, a deficit is generally observed in the depressive state, mainly with reference to phonetic fluency, although there is usually no deficit during the manias, with discordance regarding findings in patients in remission. In general, the difficulties in verbal fluency usually improve and even normalize during periods of euthymia.

Recent meta-analyses (Torres *et al*., 2007; Arts *et al*., 2008; Bora *et al*., 2009) have shown that bipolar patients present significantly lower results in executive function tests than healthy subjects. The deficits observed were not due to differences related to premorbid intelligence quotient (IQ) or years of education. The executive dysfunctions, especially in tasks requiring inhibitory control, constitute a very important trait marker of bipolar disorder, independently of the severity of the disorder and the medication. Deficits in different executive functions are present from the onset of the disease (Torres *et al*., 2010), and even the recurrence of manic episodes may have a long-term neurocognitive impact on executive function (López-Jaramillo *et al*., 2010a). On the other hand, Frangou and colleagues (2005) also found that alterations in executive function represent a trait marker for bipolar disorder, but that the factors related to these impairments are treatment with antipsychotic drugs, disease chronicity, and the level of symptomatology presented.

Therefore, the executive dysfunctions seem to persist at least in a subgroup of patients independently of the clinical state (Martínez-Arán *et al*., 2004a; Balanza-Martinez *et al*., 2005; Robinson and Ferrier, 2006; López-Jaramillo *et al*., 2010a). Some investigators have conceptualized the deficit in "frontal" function tasks as an alteration in the executive control of working memory. Executive alterations reflect the presence of underlying structural or functional neuroanatomical dysfunctions in the prefrontal cortex. Differences have been described in the general cortical or prefrontal volume, in particular, between patients and healthy subjects. According to the results of most of the studies published, alterations may be found in the dorsolateral anterior cingulate prefrontal cortex.

## Psychomotor performance

Motor performance has been scarcely studied in bipolar disorder. Greater psychomotor slowing has been described in depressive bipolar than in unipolar patients. In studies comparing euthymic bipolar patients with healthy controls, the deficit reportedly persisted during euthymia

even after controlling for the residual depressive symptoms using tests such as the TMT-A or the Digit Symbol Substitution Test (DSST). A deficit has been observed in coordination and motor sequencing. Nonetheless, other authors have not reported differences in performance between euthymic patients and controls. Some studies have described psychomotor speed deficits both in bipolar patients and in healthy first-degree relatives. Thus, together with the executive functions, psychomotor functioning is considered as a cognitive phenotype of bipolar disorder (Antila *et al.*, 2007). Study of motor speed, as well as information processing speed, needs greater attention, since it is probably affected in these patients. Future investigations are required to shed light on this aspect.

### Other cognitive functions

Although there is a lack of studies in this area to date, bipolar patients present impairments in the processing of information with emotional content; for example, with regard to recognition of facial expressions, even euthymic patients demonstrate difficulty, and it is thereby considered a stable deficit. One recent study reported that bipolar patients show a biased response, mainly towards information of negative content (Gopin *et al.*, 2011). This altered pattern of cognitive–social skills suggests a dysfunction of the neuronal circuits that mediate the emotional, social, and linguistic–pragmatic processes (appropriate social use of verbal and non-verbal language).

Despite the greater interest that has arisen concerning social cognition in bipolar disorder, a great deal remains to be investigated. Impairments have been detected in the theory of mind in euthymic bipolar patients, although it has been proposed that the deficits presented may be mediated, in part, by attention deficits or executive dysfunction. On the other hand, the evidence available seems to indicate that patients in acute phases of the disease present difficulties in decision making. Likewise, some studies have reported that patients in remission may also present difficulties of this type, although there are some discrepancies. There seems to be a relation between impairment in decision making and the history of suicide attempt, probably as a risk factor of vulnerability. Neuroimaging studies have demonstrated the involvement of the ventromedial prefrontal cortex as well as the amygdala in decision making. The processing of emotional–social information is more linked to the orbitofrontal cortex, limbic system, and, especially, the amygdala, in addition to the anterior cingulate. It is also possible that these measures are related more to psychosocial functioning, and therefore to the problems that patients may present in the social and occupational areas.

One field that has begun to be investigated in the last few years, and in which much remains to be done, is the implication of the default mode network. This network is a group of cerebral regions that collaborate among themselves and are very active during rest but deactivate for performing a cognitive task. The default mode network is located in the medial parts of the hemispheres, specifically in the medial prefrontal cortex and the posterior cingulate cortex, among other zones. The few studies that have been carried out suggest a dysfunction in the default mode network in bipolar disorder similar to what has been detected in other psychiatric disorders such as schizophrenia or autism. People with psychosis present problems at the time of disconnecting this network when it is necessary to respond to an external stimulus or concentrate on a cognitive task. Defects in activation are also detected. These may turn out to be key findings in understanding mental diseases and in finding their cerebral bases (Pomarol-Clotet *et al.*, 2012).

Table 1.1 shows the cognitive domains most affected in bipolar disorder, the anatomical structures involved, and the neuropsychological tests used.

## Factors associated with cognitive dysfunctions

Different factors are related to the clinical, pharmacological, and prognostic variables which may be directly or indirectly related to cognitive functioning in patients with bipolar disorder (Table 1.2).

**Table 1.1** Cognitive domains affected in bipolar disorder, anatomical structures involved, and neuropsychological tests used

| Neurocognitive domain | Neuroanatomical structure | Test |
|---|---|---|
| Attention | | CPT, TMT-A, WAIS-III Digit Span Forward |
| Sustained attention | Orbitofrontal lateral, dorsolateral prefrontal cortex, basal ganglia | CPT |
| Divided attention | Anterior cingulate, dorsolateral prefrontal cortex | TMT |
| Inhibition/decision making | Orbitofrontal cortex, anterior cingulate | Stroop, GO-NoGo, Iowa Gambling Test |
| Spatial/verbal working memory | Superior parietal lobe, dorsolateral prefrontal cortex | WAIS-III Digit Spatial Span, WMS-III Letter-Number sequencing, N-back |
| Verbal fluency | Prefrontal cortex | FAS (COWAT), Animal Naming |
| Motor speed/skill | Subcortical ganglia, basal ganglia | TMT-A, TMT-B |
| Memory (encoding, storage, retrieval, recall) | Hippocampus, prefrontal cortex, ventromedial prefrontal cortex, temporoparietal junction | CVLT, CVLT-II, WMS-III Logical Memory |
| **Executive function** | | |
| Logical reasoning | Left frontal cortex, temporal cortex | WCST |
| Cognitive control | Ventrolateral and dorsolateral prefrontal cortex, anterior cingulate | Stroop |
| Set shifting | Cerebellum, left dorsolateral prefrontal cortex, basal ganglia | TMT-B, WCST, Stroop |

**Table 1.2** Principal factors associated with cognitive dysfunctions in bipolar disorder

- Subclinical symptoms
- Disease duration
- Number of episodes (especially manic)
- Psychotic symptoms
- Hormonal factors
- Comorbidity (substance intake, anxiety)
- Medication
- Stress
- Sleep disorders
- Other factors (diagnostic subtype, substance abuse and dependence . . .)

## Subclinical symptoms

Most bipolar patients are symptomatic most of the time, despite following pharmacological treatment. The presence of subsyndromic symptomatolology may influence the general level of functioning. The subsyndromic symptomatology probably has a specific weight in cognitive functioning in addition to a negative influence on psychosocial functioning. However, the direction of causality is not very clear, since patients with the greatest number of psychosocial difficulties also possibly develop more depressive symptomatology. In any case, bipolar patients should be evaluated when in clinical remission to avoid the confounding effect of the affective symptoms.

## Disease duration

The years of disease evolution also seem to have a relevant role in cognitive functioning in these patients, despite the discrepancies between the different studies. Chronicity, understood as duration of the disease, has been associated with greater memory deficits, although mnemonic dysfunction may also be a predictor of chronicity. Despite the scarce longitudinal studies in this field, there are progressively more contributions on the relevance of chronicity in cognitive function in bipolar disorder. In fact, a systematic review reported that of 11 studies which had analyzed the impact of chronicity on cognitive functioning, approximately half found a relation between disease duration and different cognitive variables related to psychomotor speed, visual–spatial memory, and, in particular, verbal memory (Robinson and Ferrier, 2006).

## Number of episodes

The number of relapses presented by a bipolar patient may also have a negative influence on cognitive function. The impact, such as negative consequences on functioning and quality of life, that each episode has on cognition is by no means benign, and thus, for this and other reasons, it is important to prevent relapse. Different authors have found correlations between neuropsychological deficits and a greater number of episodes or a worse disease evolution (Robinson and Ferrier, 2006). Manic episodes seem to be associated with cognitive deficits, and they may have a neurotoxic effect mainly on the hippocampus and prefrontal cortex, reducing the number of glucocorticoid receptors and leading to greater cognitive dysfunction (Ferrier and Thompson, 2002). Several studies have observed that the greater the number of manic phases, the worse the performance in measures of verbal memory and executive functions as well as in measures of attention. Nonetheless, cognitive deficits may be present from the onset of the illness, as has been observed in a sample of patients in remission following the first manic episode. The findings compared to depressive phases are not as consistent, but 60% of the studies analyzing the relationship between depressive episodes and neuropsychological variables also found negative correlations (Robinson and Ferrier, 2006). The concept of "allostatic load" may help to explain the negative effects that repeated episodes produce, increasing and involving alterations at a molecular level that are translated into an impact on neurocognition.

## Psychotic symptoms

The presence of psychotic symptoms, or, more specifically, a previous history of psychotic symptomatology, may be associated with worse cognitive function in bipolar patients (Martínez-Arán *et al*., 2004a, 2008; Daban *et al*., 2006a). Nonetheless, contrary to this hypothesis, some findings associate the cognitive deficit in schizophrenia with negative syndromes and disorganization. Moreover, the cognitive deficit in schizophrenia is characterized by its stability, independently of the psychotic symptoms. Studies have been performed in patients with first episodes with and without psychotic symptoms, and it has been observed that those presenting psychotic symptoms, independently of the diagnosis (unipolar or bipolar disorders or schizophrenia), achieved a worse performance than patients without psychotic symptoms. Along the same lines, the findings of other studies indicate that psychotic symptomatology has a negative influence on performance in a large proportion of the neuropsychological tests, especially those related to executive functions (Bora *et al*., 2007; Glahn *et al*., 2007) and verbal memory (Martínez-Arán *et al*., 2007). A recent meta-analysis also pointed in the same direction, although the effect of the psychotic symptoms did not, by itself, explain the cognitive dysfunction in bipolar patients (Bora *et al*., 2010).

## Hormonal factors

Hypercortisolemia may be present during manic and depressive phases of bipolar disorder. Some studies have suggested that elevated cortisol levels may produce lesions in the hippocampus, even after remission of the acute episode, which may lead to dysfunctions, especially in declarative memory. Atrophy and loss of hippocampal neurons may be induced by stress.

The potential neurotoxic effects of hypercortisolemia could explain, in part, that the course of the disease may become complicated with each episode and that manic episodes may be closely related to cognitive deficits. On the other hand, one of the mechanisms contributing to the negative impact of stress is the regulation of neurotrophic factors such as BDNF (brain-derived neurotrophic factor), which is necessary for neuron survival and function. Sustained reduction of this factor contributes to the neurotoxic effect of stress on the brain. Both acute and chronic stress influences a reduction in cerebral neuroplasticity. In addition, a reduction in BDNF has been associated with poorer performance of memory tests and executive functions (Kapczinski *et al*., 2008a).

Patients medicated with lithium and presenting subclinical hypothyroidism showed worse performance in verbal learning and memory tests compared with patients without thyroid alterations (Tremont and Stern, 1997, 2000). Similar results have been obtained in other studies, observing that the side effects improve in patients treated with thyroxine and that the performance of neuropsychological tasks are more correlated with the serum levels of thyrotrophin than with those of lithium.

## Medication

The effect of pharmacological treatment is difficult to assess in bipolar patients, since they usually follow combined treatments at variable doses.

The negative effects of lithium on cognition seem to be lesser and of little importance, emphasizing the current study on the neuroprotective effects of lithium. In a recent study, no neuropsychological differences were observed when comparing patients treated with lithium monotherapy with patients without pharmacological treatment, thereby indicating that the neurocognitive deficits are not explained by the treatment (López-Jaramillo *et al*., 2010b). Likewise, in a longitudinal study over a six-year period, no differences were found between the patients receiving and not receiving lithium, demonstrating stable neuropsychological performance (Engelsmann *et al*., 1988).

With respect to anticonvulsants, there is little evidence of cognitive deficits, although a deficit in concentration has been described with valproate or carbamazepine. Among the new antiepileptics, lamotrigine and gabapentin seem to demonstrate a better cognitive profile in epileptic patients, and some preliminary data available on bipolar patients favor lamotrigine with respect to cognitive performance compared with conventional antiepileptics (Daban *et al*., 2006b).

In relation to antipsychotics, the use of conventional antipsychotics may have a negative effect on short-term motor function, although a beneficial effect may be produced in the long-term surveillance and visual processing of information. Most authors agree that antipsychotics do not improve cognitive function, but neither do they worsen it, and that even the cognitive side effects are related more to the use of anticholinergic medication than to antipsychotics. However, their effect in bipolar patients requires further study, since most research has been undertaken in schizophrenic patients. The incorporation of new antipsychotics will probably help to improve these cognitive dysfunctions, although the cognitive function will most likely not normalize in these patients.

With respect to antidepressants there is little clear evidence showing a worsening in cognitive function, and, in general, they have a positive cognitive profile, except for those in which the anticholinergic effects are greater.

Finally, benzodiazepines, which are normally used to treat insomnia and anxiety in these patients, may produce memory, attention, and motor speed dysfunctions, if the administration is prolonged.

Nonetheless, the cognitive dysfunctions observed in bipolar patients do not seem to be due only to the medication, and thus it cannot be stated that they are exclusively a pharmacologic by-product. Cognitive deficits are largely related to the disease itself, as demonstrated in the scarce

studies performed in non-medicated patients and in investigations with first-degree relatives. The truth is that most of the data referring to the effects of the medication on cognition have been achieved in samples including schizophrenic or epileptic patients and, in most cases, in healthy volunteers, but little is known about how it affects bipolar patients from a neurocognitive point of view. Although the cognitive deficit in bipolar disorder does not seem to be a primary effect of treatment, it cannot be ruled out that some treatments have a certain impact on cognitive functions, especially in the case of high doses or combined treatments.

### Other factors

Substance abuse and dependence is associated with a worse course of the disease and may affect cognitive function. Comorbid alcohol dependence has been associated with worse performance on measures of executive function and verbal memory, although the deficits are generally related more to the bipolar disorder itself than to the premorbid disorder of alcohol abuse or dependence (Sánchez-Moreno *et al*., 2009a).

Other factors which may be related to greater cognitive dysfunction are rapid cycling, although this relationship has been little studied, the number of hospitalizations indirectly associated with the severity of the course of the disease, the family history of affective or psychotic disorders, and sleep alterations, which may also influence memory function.

The diagnostic subtype is also interesting to study, given the paucity of data on this aspect; in general, studies of cognitive deficits have been undertaken either in bipolar I patients or in heterogeneous patients, including both bipolar I and II. The scientific literature suggests that bipolar II patients also present cognitive deficits, although perhaps of a lesser grade than type I patients in some cognitive domains (Torrent *et al*., 2006; Sole *et al*., 2012). There is a growing interest in the need to differentiate subgroups at a neuropsychological level. On comparing the schizoaffective disorder versus bipolar patients without psychotic symptoms and healthy controls, worse cognitive function was observed in the schizoaffective patients (Torrent *et al*., 2007). Therefore, cognitive dysfunctions are observed along the whole bipolar spectrum, supporting the hypothesis of a continuum among the affective disorders and the schizophrenic spectrum.

## Neurodevelopment or neuroprogression?

There are many doubts as to whether cognitive deficits are present prior to the onset of the disease, which would favor the hypothesis of alterations in neurodevelopment. On the other hand, it may be the impact of the disease itself that negatively influences cognition, which would support the hypothesis of cognitive impairment or a neurodegenerative process. Nonetheless, the two processes may possibly be compatible. From a neuropsychological point of view, follow-up studies of more than one year in these patients are scarce. It seems that the deficits are maintained, but it is complicated to establish whether this impairment is stable or progressive.

Some subtle neurocognitive deficits are probably present prior to the onset of the disease, although few studies have been carried out in populations at high risk of having bipolar disorder. Nonetheless, according to the findings available at present, the hypothesis of neurodevelopment seems to be the more plausible for schizophrenia than for bipolar disorder. In one of the studies undertaken in Dunedin (New Zealand), the subjects later diagnosed with bipolar disorder showed higher premorbid intellectual function than schizophrenic subjects, with a similar or even higher function than healthy controls (Cannon *et al*., 2002). Other studies carried out in Sweden and Israel showed similar findings (Reichenberg *et al*., 2002; Zammit *et al*., 2004). However, recent investigations performed in the University of Valencia and in the Institute of Neurosciences in the Miguel Hernández University in Alicante, Spain, have suggested the possibility that at least a small percentage of bipolar patients may present alterations linked to neurodevelopment. These contributions are of extraordinary interest, since they suggest that a subgroup of bipolar patents and schizophrenic patients present mutations in genes implicated in neuronal migration, and these anomalies may even predict the presence of executive dysfunctions in these patients (Tabares-Seisdedos *et al*., 2006).

In recent years, in the search for candidate endophenotypes, there has been increasing interest in the possibility that cognitive dysfunctions are also present in first-degree relatives of bipolar patients. If the neuropsychological deficits found in the patients were a phenotypic expression of genetic vulnerability to bipolar disorder, healthy subjects with a genetic predisposition for this disease would be expected to manifest the same deficits. Among the studies carried out in adults with a genetic risk of having bipolar disorder, most demonstrated mild impairments in different components of executive functions (planning, inhibition, or cognitive flexibility) and verbal memory (Thompson *et al*., 2005). Nonetheless, a recent investigation based on a multigenerational study with a wide sample of families suggested genetically correlated and significantly heritable measures related to processing speed, working memory, and declarative memory (facial) as potential endophenotypes (Glahn *et al*., 2010). Likewise, studies performed in twins of bipolar patients without the disease have shown a deficit in working memory and in delayed memory of verbal information. At the same time, worse academic performance has been observed in the children of bipolar patients, suggesting a certain grade of cognitive involvement in children in the absence of clinical symptoms but with a high risk of developing the disease. In another study, discordance was observed between verbal and manipulative IQ, with better performance in the former. These arguments imply the possibility that there are cognitive endophenotypes that are trait markers of the disease, and therefore possible biological markers in the psychopathology of bipolar disorder.

We are still in the initial stages, and it is too early to draw conclusions. Future studies will probably provide greater clarity as to whether the deficit is present prior to the onset of bipolar disorder, is a consequence of the disease itself, or is a product of the combination of the two. According to some authors, memory impairments depend more on the clinical state at an early age, and with time convert into a trait due to the neurotoxicity associated with multiple episodes which affect the functioning of the prefrontal and medial temporal cortex. This neurotoxic model would imply that through pathological levels of cortisol, multiple relapses lead to neurostructural changes, which may be accompanied by cognitive dysfunctions that persist after clinical remission. The patient recovers from the episode, but the anatomical alterations undergo a slow recovery or may even be irreversible. At present, however, this interpretation remains speculative, and further, more rigorous, investigations are required to confirm the hypothesis.

With regard to the early phases, deficits in sustained attention, learning and memory, spatial reasoning, and in some executive functions have been described in euthymic patients following the first episode of mania. In one of these studies the cognitive deficit was associated more with the fact of having presented psychotic symptoms during the episode than with the diagnosis. In another study with a two-year follow-up after the first affective episode, bipolar patients presented very few cognitive dysfunctions.

The great problem in the study of the evolution of cognitive dysfunctions in bipolar disorder is that these have been studied from a cross-sectional perspective, and few longitudinal follow-ups of more than one year have been performed, although there are some, albeit very few, studies which have evaluated patients in the acute phase and in remission around one year and eight months later. None of these studies found progressive cognitive impairment. In stable patients, Balanza-Martinez and collaborators (2005) observed persistent deficits in 12 of the 13 cognitive measures compared with normal controls. Other data from a two-year follow-up study in euthymic bipolar patients treated largely with lithium monotherapy can be added to these data (Mur *et al*., 2008). The findings suggest persistent deficits in executive functions and processing speed, despite an average time of euthymia of three years in this sample. These results suggest that neurocognitive deficits are maintained even when the inter-episode periods are prolonged. In another longitudinal study with a mean follow-up of nine years, persistence in cognitive deficits was observed in all the domains except in the executive functions, in which a worsening was described (Torrent *et al*., 2012).

It is evident that more longitudinal studies are required to elucidate the evolution of cognitive dysfunctions in bipolar patients, since the data obtained to date are too scarce to conclude that the deficits worsen over time. Indeed, the most we can say is that the deficits persist in the long term. One of the most consistent findings is that the dysfunctions, especially in verbal memory