frontiers in Physiology

REVIEW
published: 07 April 2015
doi: 10.3389/fphys.2015.00108

Bipolar disorder comorbid with alcohol use disorder: focus on neurocognitive correlates

Vicent Balanzá-Martínez[1], Benedicto Crespo-Facorro[2], Ana González-Pinto[3] and Eduard Vieta[4]*

[1] Teaching Unit of Psychiatry, Deparment of Medicine, School of Medicine, La Fe University and Polytechnic Hospital, University of Valencia, CIBERSAM, ISNPR, Valencia, Spain, [2] Department of Psychiatry, School of Medicine, University Hospital Marqués de Valdecilla, University of Cantabria-IDIVAL, CIBERSAM, Santander, Spain, [3] Álava University Hospital, CIBERSAM, University of the Basque Country, Kronikgune, Vitoria, Spain, [4] Barcelona Bipolar Disorders Program, Institute of Neurosciences, University of Barcelona, IDIBAPS, CIBERSAM, Barcelona, Spain

Bipolar disorder (BD) and alcohol use disorders (AUDs) are usually comorbid, and both have been associated with significant neurocognitive impairment. Patients with the BD-AUD comorbidity (dual diagnosis) may have more severe neurocognitive deficits than those with a single diagnosis, but there is paucity of research in this area. To explore this hypothesis more thoroughly, we carried out a systematic literature review through January 2015. Eight studies have examined the effect of AUDs on the neurocognitive functioning of BD patients. Most studies found that BD patients with current or past history of comorbid AUDs show more severe impairments, especially in verbal memory and executive cognition, than their non-dual counterparts. Greater neurocognitive dysfunction is another facet of this severe comorbid presentation. Implications for clinical practice and research are discussed. Specifically, the application of holistic approaches, such as clinical staging and systems biology, may open new avenues of discoveries related to the BD-AUD comorbidity.

Keywords: bipolar disorder, comorbidity, addiction, alcohol use disorders, neurocognition, staging, systems biology

OPEN ACCESS

Edited by:
Anaïs Baudot, Centre National de la Recherche Scientifique, France

Reviewed by:
KP Su, China Medical University, Taiwan
Miguel Ruiz-Veguilla, Universidad de Sevilla/CSIC, Spain

****Correspondence:***
Vicent Balanzá-Martínez, Teaching Unit of Psychiatry and Psychological Medicine, Department of Medicine, University of Valencia-CIBERSAM, Avda Blasco Ibáñez, 15, 46010 Valencia, Spain
vicente.balanza@uv.es

Specialty section:
This article was submitted to Systems Biology, a section of the journal Frontiers in Physiology

Received: *24 January 2015*
Accepted: *17 March 2015*
Published: *07 April 2015*

Citation:
Balanzá-Martínez V, Crespo-Facorro B, González-Pinto A and Vieta E (2015) Bipolar disorder comorbid with alcohol use disorder: focus on neurocognitive correlates. Front. Physiol. 6:108. doi: 10.3389/fphys.2015.00108

Neurocognitive Dysfunction is a Core Feature of Bipolar Disorder

Bipolar disorder (BD) is associated with significant morbidity, premature mortality and functional disability (Salomon et al., 2013; Conus et al., 2014). The major sources of this disability seem to be episode density, psychotic features, subclinical depression, sustained neurocognitive deficits, comorbidities, medication side effects, low premorbid functioning and weak social support (Sanchez-Moreno et al., 2009a).

It is well established that BD is associated with neurocognitive deficits that persist into euthymia after episode resolution, and thus represent a core symptom of the illness (Balanzá-Martínez and Dias, 2013). Several meta-analysis have revealed impairments in the broad domains of attention, processing speed, verbal memory and executive functions, with relative preservation of verbal abilities and intelligence (Torres et al., 2007; Bora et al., 2009; Bourne et al., 2013). This pattern of deficits is similar to that in schizophrenia (SZ), although less severe in magnitude (Daban et al., 2006; Sánchez-Morla et al., 2009). The variability in the degree and pattern of cognitive functioning among BD patients is also more pronounced than in

SZ, and it has been estimated that 30–60% of euthymic BD patients show clinically relevant deficits (Martino et al., 2008). Moreover, in population-based studies, BD has been associated with increased risk for later development of dementia, especially in middle-age adults (Wu et al., 2013). This risk seems to increase with the number of episodes (Kessing and Andersen, 2004) and is independent of confounding variables such as comorbidities (Wu et al., 2013).

There is also growing evidence that neurocognitive impairments are major predictors of BD patients' long-term functional outcomes (Tabarés-Seisdedos et al., 2008; Wingo et al., 2009). Therefore, neurocognitive improvement represents a therapeutic target in BD (Fuentes-Durá et al., 2012). There is pressing need to develop interventions specifically addressed to ameliorate these deficits by means of pro-cognitive medications (Dias et al., 2012) and cognitive training and rehabilitative strategies, such as functional remediation (Torrent et al., 2013).

Persistent neurocognitive deficits (Balanzá-Martínez et al., 2005) likely result from the combination of genetic and environmental risk factors, as well as neurodevelopmental and neuroprogressive processes (Goodwin et al., 2008). Neurocognitive impairment may increase with illness progression (Robinson and Ferrier, 2006; Bourne et al., 2013) and history of psychotic symptoms (Selva et al., 2007; Martínez-Arán et al., 2008; Brissos et al., 2011), but it is also found in healthy first-degree relatives of patients with BD, although at a lesser degree (Arts et al., 2008; Balanzá-Martínez et al., 2008). Subsyndromal depressive symptoms, comorbidites and side effects of medications may compound and further worsen these deficits yet cannot fully explain them (Balanzá-Martínez et al., 2010).

The relative contribution of psychiatric comorbidities to BD patients' neurocognition has received limited attention. Dual diagnosis is the concomitant or comorbid presentation of a substance use disorder (SUD) or an alcohol use disorder (AUD) and another psychiatric condition. Patients with dual diagnosis represent a clinical population of special interest because BD is highly comorbid with addictions (Cerullo and Strakowski, 2007; Schoepf and Heun, 2014) and prolonged heavy use of alcohol and other substances is associated with persistent neurocognitive and brain abnormalities (Cunningham and McCambridge, 2012). Clearly, this relevant issue requires further examination.

The Bipolar—Alcohol Comorbidity

Several epidemiological and clinical studies have consistently found high rates of comorbid AUD (i.e., alcohol abuse or dependence) among BD patients (Merikangas et al., 2007; Mitchell et al., 2007; Oquendo et al., 2010). Indeed, BD is the DSM Axis I disorder most strongly associated with AUDs (Regier et al., 1990; Kessler et al., 1997). In a recent meta-analysis, lifetime prevalence of AUDs affected approximately one third of BD patients, with higher rates in male (44%) than in female (22%) patients (Di Florio et al., 2014). Overall, patients with addictions are 5–6 times more likely to have a history of BD compared to the general population (Kessler et al., 1997). Research has identified three subgroups of patients, presenting with AUD first, BD first, and both simultaneously. BD preceded by addiction may represent a milder illness form (Pacchiarotti et al., 2009).

Although the etiology of the BD-AUD comorbidity is poorly understood, several explanations have been put forward. Both BD and AUD are complex-trait conditions with overlapping etiopathophysiological pathways at the genetic, neurochemical, neurophysiologic and neuroanatomic levels (Farren et al., 2012). Shared genetic basis could confer risk for both BD and AUD (Johnson et al., 2009). Interestingly, this common genetic vulnerability would not be entirely driven by confounders, such as liability for anxiety disorders (Carmiol et al., 2014). Moreover, comorbid alcohol and substance use may also be a coping strategy by which patients try to manage (e.g., by self-treatment) their mood symptoms (Bizzarri et al., 2009; Do and Mezuk, 2013). BD and addictions may share common mechanisms, including high impulsivity, executive dysfunction, susceptibility to behavioral sensitization to stressors, as well as poor modulation of motivation and responses to rewarding stimuli (Swann, 2010; Tolliver and Hartwell, 2012). Indeed, high trait impulsivity may mediate some severe manifestations of this comorbidity (Swann et al., 2009; Nery et al., 2013).

At the clinical level, dual diagnosis seems to be mutually detrimental since addiction worsens the clinical presentation, course, prognosis and treatment of BD, and vice versa (Salloum and Thase, 2000). Compared to BD patients without addictions, dually diagnosed patients have earlier age of onset, poor treatment adherence and treatment response, longer and more frequent mood episodes and hospitalizations, more mixed episodes and rapid cycling, more comorbid anxiety disorders and greater impulsivity, and higher rates of aggressive behavior and suicide attempts (Swann, 2010; Tolliver and Hartwell, 2012; Nery et al., 2013). Comorbid addictions worsen functioning in BD, sometimes to that of SZ patients (Jaworski et al., 2011). Clearly, dual BD represents a prevalent, severe and difficult to treat subgroup of BD, but, surprisingly, little is known about its neurobiological and neurocognitive correlates (Nery et al., 2011).

The Neurocognitive Dysfunction Associated with Alcohol Use Disorders

Chronic alcoholism exerts harmful effects on brain health and cognition, including significantly decreased cortical thickness (Momenan et al., 2012). In addition to brain atrophy, enlargement of the ventricles and sulci, as well as reductions in cerebral blood flow and glucose metabolism, particularly in prefrontal areas, have been described (Gupta and Warner, 2008). Moreover, chronic alcohol misuse has been consistently associated with widespread neurocognitive deficits, including episodic memory, attention, processing speed, visuospatial and motor abilities, verbal fluency, and executive functions, such as decision-making, problem-solving, working memory, and mental flexibility (Stavro et al., 2013; Bernardin et al., 2014). According to a recent meta-analysis, all these deficits were of moderate magnitude and IQ was the only domain not significantly affected by chronic alcoholism (Stavro et al., 2013). As many as 50-80% of patients show neurocognitive impairment, although there exists marked

inter-individual variability in the nature and the severity of deficits (Bates et al., 2002; Bernardin et al., 2014). For instance, treatment-resistant heavy drinkers have more severe executive dysfunctions (Wollenweber et al., 2014). In the most severe and chronic cases, the clinical presentation may be dominated by cognitive features, such as confabulation, amnesia and confusional states (e.g., Wernicke-Korsakoff syndrome), as well as global cognitive deterioration (e.g., alcohol-related dementia).

Prospective studies suggest that abstinence from alcohol results in partial neurocognitive recovery, especially regarding sustained attention (Schulte et al., 2014). Overall, a widespread pattern of impairment seems to remain stable during the first year of sobriety and neurocognitive performance tends to normalize only after 1 year of abstinence (Stavro et al., 2013). However, certain functions, such as visuospatial abilities, may remain persistenly impaired even after longer periods of abstinence (Bernardin et al., 2014). Therefore, several memory rehabilitation strategies have been developed, although the field is still in its infancy (Svanberg and Evans, 2013).

Here we aim to review the literature that has examined the relative contribution of AUDs to the neurocognitive functioning of BD patients. Since both BD and AUDs have been associated with neurocognitive impairment on their own, patients with the BD-AUD comorbidity (e.g., dual diagnosis) may have more severe neurocognitive deficits than those with a single diagnosis.

To explore this hypothesis more thoroughly, we carried out a systematic literature review. Electronic databases (PubMed, Scopus, EMBASE) were searched through January 2015 using combinations of the following search terms: *bipolar disorder* cross-referenced with *cognition*, *neurocogniti** or *neuropsycholog** cross-referenced with *alcohol use disorder, alcohol abuse* or *alcohol dependence*. These searches retrieved 23, 63, and 389 hits, respectively. In addition, the reference lists of relevant papers were manually checked for further articles not previously identified. Studies comparing neuropsychological performance of BD subjects with/without AUDs were selected.

The Relative Contribution of Comorbid Alcohol Use Disorders

So far, only eight studies met the selection criteria and have compared the neurocognitive functioning of BD patients with and without comorbid AUDs (van Gorp et al., 1998; Levy et al., 2008, 2012; Sanchez-Moreno et al., 2009b; van der Werf-Eldering et al., 2010; Shan et al., 2011; Chang et al., 2012; Marshall et al., 2012). The major characteristics of these studies are shown in **Table 1**.

In a pioneer work, van Gorp et al. (1998) examined 12 BD patients with past history of alcohol dependence, 13 BD patients without such comorbidity, and 22 healthy controls. Only males were recruited and all outpatients were euthymic at the time of neurocognitive assessment. Both BD groups showed verbal memory deficits, whereas only the dual group had an additional executive deficit measured by the number of completed categories in the Wisconsin Card Sorting Test (WCST). Moreover, neurocognitive functioning was negatively correlated with lifetime duration of manic or depressive episodes, suggesting that patients with greater illness burden had poorer performances.

Interestingly, it took one decade for the field to revisit this topic. Levy et al. (2008) compared three groups of BD-I inpatients, who were admitted mostly due to manic episodes. A first group with current alcohol dependence ($n = 13$), a second group in full remission (e.g., during at least 1 year) from alcohol dependence ($n = 9$), and a third non-dual group without history of SUDs ($n = 41$). Those with current alcohol dependence were significantly more impaired than the non-dual group in measures of visual memory and verbal memory. Moreover, both dual BD groups performed significantly worse than non-dual BD patients on executive functions measured by the Stroop test and WCST. These findings would suggest that the BD-AUD comorbidity is associated with more severe mnemonic and executive dysfunction, and that the neurocognitive consequences of past AUDs may persist despite sustained abstinence from alcohol. However, the presence of subacute, residual mood symptoms during examination before hospital discharge may increase the severity of deficits found in this study.

Another study by the same research group focused on cognition during the course of early remission from a severe mood episode (Levy et al., 2012). This 3-month, follow-up study compared 21 BD patients with AUDs in the previous year and 34 BD patients without a history of SUDs. Dually diagnosed patients performed worse on measures of verbal memory, visual memory, and executive functioning on both assessments and showed a poorer neurocognitive recovery relative to those without SUDs. These findings underscore the special needs of BD-AUD patients in terms of intensive treatment and support aimed to achieve early recovery after relapses. To that end, detailed and serial neuropsychological evaluations during this critical period remain as a backbone.

Consistently, another study (Sanchez-Moreno et al., 2009b) found that euthymic BD patients with ($n = 30$) and without ($n = 35$) previous history of AUDs performed poorer than healthy controls ($n = 35$) in verbal memory and executive functions, regardless alcohol history. However, patients with previous alcohol misuse were more impaired in the Stroop interference task, suggesting greater difficulties in the inhibitory control of inadequate behaviors, which may be related to higher impulsivity and probably to higher risk of other addictive behaviors. Dual patients were requested to be abstinent for at least 1 year but time of abstinence was not recorded. BD-II patients were also recruited, and this is particularly relevant since type II is also significantly associated with neurocognitive impairments and AUDs (McElroy et al., 2001; Solé et al., 2012).

In this regard, a Taiwanese study focused only on type-II BD (Shan et al., 2011). The authors compared 19 patients with comorbid AUD, 28 patients without comorbid AUD, and 22 healthy controls. All participants were alcohol-free at least 24 h before examination and BD patients were euthymic. Compared to the other two groups, dual patients performed significantly worse on tasks of visual memory, verbal memory, attention, psychomotor speed, and executive functioning. In addition, working memory was impaired in both BD groups, although more so in dual patients. However, the clinical groups were not balanced regarding gender, educational level and number of hospitalizations, so a potential influence of these relevant

TABLE 1 | Main characteristics of studies included in the review.

Study	Country	Sample description		Measures of alcohol consumption	Urine screening test to exclude other SUDs	Specific comments
		Type of BD	Phase of BD			
van Gorp et al., 1998	USA	25 BD (type not specified) - 12 with past AD - 13 without AD 22 HC	All patients euthymic (HRSD<7 and YMRS<6 for 3 consecutive monthly assessments)	None	Yes	Dual patients should be abstinent at least 6 months (mean duration > 8 years) All subjects were male
Levy et al., 2008	USA	63 BD (all type I) - 13 with current AD (past 6 months) - 9 with remitted AD - 41 without history of SUD No HC	All inpatients with acute mood episodes BDI <15, BHS <10 and YMRS <15	Quantity and frequency (e.g., number of standard alcoholic drinks consumed in the past month, days alcohol was used in the past month)	No	Detoxification upon admission was not required for patients with current AD History of SUD other than alcohol was allowed for the dual groups Substance use measures (ASI, AUDIT)
Sanchez-Moreno et al., 2009b	Spain	65 BD (51 type I) - 30 with history of AB/AD - 35 without AB/AD 35 HC	All euthymic outpatients with 6 consecutive months of remission (HRSD $\leq$ 8 and YMRS $\leq$ 6)	None	Yes	Dual patients should be abstinent for at least 1 year History of SUD other than alcohol was excluded as per DSM
van der Werf-Eldering et al., 2010	Netherlands	110 BD (91 type I, 19 type II) - 21 with lifetime AUD (13 with current AUD) 75 HC	Outpatients either euthymic ($n = 46$) or with mild or moderate depressive symptoms ($n = 64$) Severe depressive symptoms (IDS>38) and manic symptoms (YMRS>7) were exclusion criteria	None	No	Patients with severe AUD (currently needing treatment in specialized setting) were excluded
Shan et al., 2011	Taiwan	69 BD (all type II) - 19 BD with history of AB/AD - 28 BD without AB/AD 22 HC	All patients in remission for at least 2 weeks (HRSD < 7 and YMRS < 6)	For dual patients: g/day	No	History of SUD other than alcohol was excluded as per DSM Duration of abstinence was not reported
Chang et al., 2012	Taiwan	38 BD-I: - 16 with comorbid AD - 22 without history of AD 56 BD-II - 18 with comorbid AD - 38 without history of AD 29 HC	Same as Shan et al., 2011	None	No	Same as Shan et al., 2011 All subjects were male
Levy et al., 2012	USA	55 BD (all type I) - 21 with comorbid AD (previous year) - 34 without SUD No HC	At baseline, all inpatients with acute mood episodes (34 mania, 12 mixed, 9 depression)	Same as Levy et al., 2008	Yes (only at 3-month follow-up)	Detoxification upon admission was not required for patients with AD History of SUD other than alcohol was allowed for the dual group

(Continued)

TABLE 1 | Continued

Study	Country	Sample description		Measures of alcohol consumption	Urine screening test to exclude other SUDs	Specific comments
		Type of BD	Phase of BD			
Marshall et al., 2012	USA	256 BD (201 type I, 36 type II, 19 NOS) - 158 with history of SUD (130 with alcohol) - 98 without SUD 97 HC	Outpatients and inpatients without manic symptoms (YMRS ≤ 7)	None	No	Almost half of the SUD group met criteria for multiple substances Subjects with active or current substance dependence were excluded

AB, alcohol abuse; AD, alcohol dependence; ASI, Addiction Severity Index; AUD, Alcohol Use Disorder; AUDIT, Alcohol Use Disorder Identification Test; BD, bipolar disorder; BDI, Beck Depression Inventory; BHS, Beck Hopelessness Scale; DSM-IV, Diagnostic and Statistical Manual—4th edition; HC, healthy control; HRSD, Hamilton Rating Scale for Depression; IDS, Inventory of Depressive Symptomatology; NOS, not otherwise specified; SUD, substance use disorder; YMRS, Young Mania Rating Scale.

variables on neurocognitive results cannot be entirely ruled out.

A subsequent study from the same research group (Chang et al., 2012) explored whether the neurocognitive effects of comorbid AUD is similar or different depending on the type of BD. To this end, BD-AUD patients (type I = 16; type II = 18) were compared with non-dual BD patients (type I = 22; type II = 38). The four clinical groups showed widespread neurocognitive deficits compared to healthy controls ($n = 29$) even during euthymia. Dually diagnosed patients performed significantly worse than non-dual BD patients. Of note, non-dual BD-I patients showed widespread deficits, especially in tests of attention/concentration and working memory and, whereas non-dual BD-II patients performed similarly to controls. The authors concluded that alcohol misuse seems to exert greater neurocognitive impact on BD-I. However, only male patients were recruited in this study and subjects from Asia have specific features related to alcohol consumption.

In the study with the largest sample ($n = 353$) so far, Marshall et al. (2012) evaluated 98 non-dual BD patients, 158 BD patients with comorbid addictions (130 of whom had AUDs) and 97 healthy subjects. Compared to controls, BD patients had a widespread dysfunction in areas of motor speed and dexterity, visual memory, processing speed and verbal fluency. Moreover, the dual group performed significantly worse than the non-dual group on tasks of visual memory and reasoning.

On the contrary, only one study has concluded that alcoholism was not associated with neurocognition among 185 BD patients (van der Werf-Eldering et al., 2010). However, this result was based on a *post-hoc* analysis. Moreover, the authors did not aim to compare dual and non-dual patients and even the rate of comorbid AUDs was not reported.

Implications for Clinical Practice and Research

Taken together, most studies have found that BD patients with current or past history of comorbid AUDs show more severe and/or widespread neurocognitive deficits than their non-dual counterparts. Although there is marked variability in the findings, this impairment mostly involves the broad domains of verbal memory and executive cognition. Moreover, the reviewed literature further confirms that BD itself (e.g., non-dual BD) is associated with a significant neurocognitive dysfunction, regardless mood state (Kurtz and Gerraty, 2009; Bourne et al., 2013). Cognitive dysfunction would be another phenotypic dimension common to BD and AUD. Collectively, these findings imply either that alcohol misuse poses an additional neurocognitive tax to that intrinsic to BD itself or that the BD-AUD comorbidity is a more severe form of illness associated with greater cognitive dysfunction.

The conclusion of this systematic review must be regarded as tentative given the reduced number and heterogeneity of extant studies. The former may result from neuropsychological studies usually excluding patients based on concurrent or recent misuse of alcohol and other substances. Several methodological aspects of the original studies must be also limit the generalization of

present findings. Firstly, the sample size in most cases is relatively modest, especially regarding the comorbid BD-AUD groups, which may reflect the difficulty in recruiting clinically stable and motivated patients who consent going through burdensome evaluations. Secondly, the timing of examination widely differs between studies and not all of them have assessed patients during euthymia. Doing so is currently considered a gold standard in neurocognitive research of BD (Bourne et al., 2013), but the distinct features of dual patients likely advices a less stringent approach. In this regard, proximity to an acute episode, as well as use of higher doses and combinations of pharmacological agents during admissions have been associated with worse neurocognitive performances (Balanzá-Martínez et al., 2010). Thirdly, key clinical variables, such as number of past episodes and, more importantly, time of abstinence were not recorded in all studies. Fourthly, the recruitment of homogenous samples according to gender or race may introduce another bias. Methodological refinement and standardization of procedures would allow gaining a deeper understanding of this phenomenon. Fifthly, concomitant addiction to other substances, such as cannabis, may also contribute to neurocognitive dysfunctions in BD (Cahill et al., 2006) and are beyond the scope of the present review. Similarly, complex patterns may also result from interactions with medical comorbidities and deserve further study. Cardiovascular and metabolic conditions, such as hypertension or type 2 diabetes, which are usually comorbid with both BD and AUD, are well known risk factors for cognitive deterioration (Durazzo et al., 2008). Lastly, except a 3-month follow-up study (Levy et al., 2012), most research so far has been cross-sectional. Therefore, longitudinal designs will aid to better establish the temporal relationship between neurocognitive status and the clinical features of BD and AUD.

At the clinical level, the present findings have several implications for diagnosis, treatment and prognosis. Comorbid addictive disorders, including AUDs, are a potentially treatable risk factor. Early detection and intervention is a pressing need in BD (Conus et al., 2014), and this clearly turns mandatory for dual BD, especially among young people (Hermens et al., 2013). The ultimate goal of treatments is to improve patients' functional outcomes and quality of life. This seems achievable since remission from both alcohol dependence and BD has been associated with significant improvements in quality of life compared to non-remission (Rubio et al., 2013). Moreover, absence of AUD was associated with better neurocognitive recovery during the early course of BD (Torres et al., 2014). However, few pharmacological and behavioral interventions have effectively addressed the clinical management of dual populations, probably because they may not be well-suited for this cognitively-impaired population (Bradizza et al., 2014). Indeed, neurocognitive dysfunction may represent a barrier for dual patients to benefit from psychosocial treatments, and probably also from pharmacological agents through indirect effects on diminished adherence (Martinez-Aran et al., 2009; Vieta et al., 2012; Jónsdóttir et al., 2013; Fagan et al., 2015). Preventative and treatment strategies should target neurocognitive dysfunction as a major driver of patients' functional outcomes (Tabarés-Seisdedos et al., 2008).

These findings also suggest that future neurocognitive studies of BD should take into account the potential confounding effects of comorbid AUDs, including past exposures to psychoactive substances (Savitz et al., 2005). In our opinion, two additional implications for research merit further discussion. Cosci and Fava (2011) have recently proposed an alternative strategy to examine dual diagnosis based on clinimetric methods, helped by staging and evaluation of subclinical symptoms. According to these authors, clinical staging may provide a more holistic approach to dual BD patient's problematic areas, including neurocognitive dysfunctions. Here we suggest that BD-AUD may similarly benefit from the application of another holistic perspective—systems biology.

Several staging models have been put forward to explain the progressive deterioration that takes place in a significant proportion of BD patients (Kapczinski et al., 2014). Comorbid conditions, including addictions, are predicted to be associated with greater illness progression, chronicity and deterioration (Kapczinski et al., 2009). Kindling, sensitization and allostatic load may explain the progressive course and negative outcomes of dual BD (Post and Kalivas, 2013; Pettorruso et al., 2014). Early life (e.g., childhood) adversity and stressors play a major role in the onset and relapses of both BD and AUD, and also explain the high comorbidity between them (Post and Leverich, 2006; Post and Kalivas, 2013).

However, no study has examined the neurocognitive burden of comorbid AUDs according to clinical staging (e.g., comparing early- vs. late-stage BD patients). On the other hand, few staging models for addictions exist (Langenbucher and Chung, 1995; Favrat et al., 2002) and none has been developed specifically for dual diagnosis (Cosci and Fava, 2011). In all, we propose the application of staging to better understand the neurocognitive dysfunction associated with either BD or AUD alone, and their comorbid presentation.

A systems biology approach, integrating –omics data with bioinformatical tools, aims to gain deeper insights into the etiopathophysiology of a certain disease, which in turn may provide new therapeutic targets that should be translated into clinical practice (Hoertel et al., 2013). The potential relevance of systems medicine for AUD (Spanagel et al., 2013; Gorini et al., 2014) and BD (Frangou, 2014; McIntyre et al., 2014) has been recently proposed. We agree with McIntyre et al. (2014) that this approach may be particularly relevant for BD with comorbid conditions. Specifically, systems biology provides an exciting opportunity to better understand the BD-AUD comorbidity at different levels. Unraveling the genes and proteins involved in the vulnerability to BD-AUD is relevant to inform on the subserving molecular and cellular mechanisms and to identify novel treatments and molecules for the management of this comorbidity. This is clearly relevant since many dual BD patients may receive suboptimal treatments. This approach may also prove fruitful to refine current nosology of dual diagnosis based on more biologically informed grounds (Frangou, 2014).

In sum, the bipolar-addiction comorbidity may benefit from the application of holistic approaches, such as staging and systems biology.

Author Contributions

All the authors have been sufficiently involved in the submitted study and have approved the final paper.

Acknowledgments

The authors of this report would like to acknowledge the support of the Spanish Ministry of Economy and Competitiveness, Instituto de Salud Carlos III (ISCIII), CIBERSAM. This work was sponsored by a national grant PI14/00894 which belongs to the Spanish "Plan Nacional de I+D+I 2013-2016" and is co-funded by the "ISCIII-Subdirección General de Evaluación y el Fondo Europeo de Desarrollo Regional (FEDER)."

References

Arts, B., Jabben, N., Krabbendam, L., and van Os, J. (2008). Meta-analyses of cognitive functioning in euthymic bipolar patients and their first-degree relatives. *Psychol. Med.* 38, 771–785. doi: 10.1017/S0033291707001675

Balanzá-Martínez, V., and Dias, V. V. (2013). "Neurocognitive dysfunction in bipolar disorder," in Clinical Management of Bipolar Disorder, ed P. B. Mitchell (Future Medicine), 78–86.

Balanzá-Martínez, V., Rubio, C., Selva–Vera, G., Martínez–Aran, A., Sánchez–Moreno, J., Salazar–Fraile, J., et al. (2008). Neurocognitive endophenotypes (endophenocognitypes) from studies of relatives of bipolar disorder subjects: a systematic review. *Neurosci. Biobehav. Rev.* 32, 1426–1438. doi: 10.1016/j.neubiorev.2008.05.019

Balanzá-Martínez, V., Selva, G., Martínez-Arán, A., Prickaerts, J., Salazar, J., González-Pinto, A., et al. (2010). Neurocognition in bipolar disorders—a closer look at comorbidities and medications. *Eur. J. Pharmacol.* 626, 87–96. doi: 10.1016/j.ejphar.2009.10.018

Balanzá-Martínez, V., Tabarés-Seisdedos, R., Selva-Vera, G., Martínez-Arán, A., Torrent, C., Salazar-Fraile, J., et al. (2005). Persistent cognitive dysfunctions in bipolar—I and schizophrenic patients: a 3-year follow-up study. *Psychother. Psychosom.* 74, 113–119. doi: 10.1159/000083170

Bates, M. E., Bowden, S. C., and Barry, D. (2002). Neurocognitive impairment associated with alcohol use disorders: implications for treatment. *Exp. Clin. Psychopharmacol.* 10, 193–212. doi: 10.1037/1064-1297.10.3.193

Bernardin, F., Maheut-Bosser, A., and Paille, F. (2014). Cognitive impairments in alcohol-dependent subjects. *Front. Psychiatry* 5:78. doi: 10.3389/fpsyt.2014.00078

Bizzarri, J. V., Rucci, P., Sbrana, A., Miniati, M., Raimondi, F., Ravani, L., et al. (2009). Substance use in severe mental illness: self-medication and vulnerability factors. *Psychiatry Res.* 165, 88–95. doi: 10.1016/j.psychres.2007.10.009

Bora, E., Yucel, M., and Pantelis, C. (2009). Cognitive endophenotypes of bipolar disorder: a meta-analysis of neuropsychological deficits in euthymic patients and their first-degree relatives. *J. Affect. Disord.* 113, 1–20. doi: 10.1016/j.jad.2008.06.009

Bourne, C., Aydemir, Ö., Balanzá-Martínez, V., Bora, E., Brissos, S., Cavanagh, J. T.O., et al. (2013). Neuropsychological testing of cognitive impairment in euthymic bipolar disorder: an individual patient data meta-analysis. *Acta Psychiatr. Scand.* 128, 149–162. doi: 10.1111/acps.12133

Bradizza, C. M., Stasiewicz, P. R., and Dermen, K. H. (2014). Behavioral interventions for individuals dually-diagnosed with a severe mental illness and a substance use disorder. *Curr. Addict. Rep.* 1, 243–250. doi: 10.1007/s40429-014-0032-9

Brissos, S., Dias, V. V., Soeiro-de-Souza, M. G., Balanzá-Martínez, V., and Kapczinski, F. (2011). The impact of a history of psychotic symptoms on cognitive function in euthymic bipolar patients: a comparison with schizophrenic patients and healthy controls. *Rev. Bras. Psiquiatr.* 33, 353–361. doi: 10.1590/S1516-44462011000400008

Cahill, C. M., Malhi, G. S., Ivanovski, B., Lagopoulos, J., and Cohen, M. (2006). Cognitive compromise in bipolar disorder with chronic cannabis use: cause or consequence? *Expert Rev. Neurother.* 6, 591–598. doi: 10.1586/14737175.6.4.591

Carmiol, N., Peralta, J. M., Almasy, L., Contreras, J., Pacheco, A., Escamilla, M. A., et al. (2014). Shared genetic factors influence risk for bipolar disorder and alcohol use disorders. *Eur. Psychiatry* 29, 282–287. doi: 10.1016/j.eurpsy.2013.10.001

Cerullo, M. A., and Strakowski, S. M. (2007). The prevalence and significance of substance use disorders in bipolar type I and II disorder. *Subst. Abuse Treat Prev. Policy* 2:29. doi: 10.1186/1747-597X-2-29

*Chang, Y. H., Chen, S. L., Lee, S. Y., Hsu, Y. W., Wu, J. Y., Chen, S. H., et al. (2012). Neuropsychological functions in bipolar disorders I and II with and without comorbid alcohol dependence. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 37, 211–216. doi: 10.1016/j.pnpbp.2012.01.015

Conus, P., Macneil, C., and McGorry, P. D. (2014). Public health significance of bipolar disorder: implications for early intervention and prevention. *Bipolar Disord.* 16, 548–556. doi: 10.1111/bdi.12137

Cosci, F., and Fava, G. A. (2011). New clinical strategies of assessment of comorbidity associated with substance use disorders. *Clin. Psychol. Rev.* 31, 418–427. doi: 10.1016/j.cpr.2010.11.004

Cunningham, J. A., and McCambridge, J. (2012). Is alcohol dependence best viewed as a chronic relapsing disorder? *Addiction* 107, 6–12. doi: 10.1111/j.1360-0443.2011.03583.x

Daban, C., Martínez-Arán, A., Torrent, C., Tabarés-Seisdedos, R., Balanzá-Martínez, V., Salazar-Fraile, J., et al. (2006). Specificity of cognitive deficits in bipolar disorder versus schizophrenia. A systematic review. *Psychother. Psychosom.* 75, 72–84. doi: 10.1159/000090891

Dias, V. V., Balanzá-Martinez, V., Soeiro-de-Souza, M. G., Moreno, R. A., Figueira, M. L., Machado-Vieira, R., et al. (2012). Pharmacological approaches in bipolar disorders and the impact on cognition: a critical overview. *Acta Psychiatr. Scand.* 126, 315–331. doi: 10.1111/j.1600-0447.2012.01910.x

Di Florio, A., Craddock, N., and van den Bree, M. (2014). Alcohol misuse in bipolar disorder. A systematic review and meta-analysis of comorbidity rates. *Eur. Psychiatry* 29, 117–124. doi: 10.1016/j.eurpsy.2013.07.004

Do, E. K., and Mezuk, B. (2013). Comorbidity between hypomania and substance use disorders. *J. Affect. Disord.* 150, 974–980. doi: 10.1016/j.jad.2013.05.023

Durazzo, T. C., Rothlind, J. C., Gazdzinski, S., and Meyerhoff, D. J. (2008). The relationships of sociodemographic factors, medical, psychiatric, and substance-misuse co-morbidities to neurocognition in short-term abstinent alcohol-dependent individuals. *Alcohol* 42, 439–449. doi: 10.1016/j.alcohol.2008.06.001

Fagan, C. S., Carmody, T. J., McClintock, S. M., Suris, A., Nakamura, A., Jeon-Slaughter, H., et al. (2015). The effect of cognitive functioning on treatment attendance and adherence in comorbid bipolar disorder and cocaine dependence. *J. Subst. Abuse Treat.* 49, 15–20. doi: 10.1016/j.jsat.2014.06.008

Farren, C. K., Hill, K. P., and Weiss, R. D. (2012). Bipolar disorder and alcohol use disorder: a review. *Curr. Psychiatry Rep.* 14, 659–666. doi: 10.1007/s11920-012-0320-9

Favrat, B., Rao, S., O'Connor, P. G., and Schottenfeld, R. (2002). A staging system to predict prognosis among methadone maintenance patients, based on admission characteristics. *Subst. Abus.* 23, 233–244. doi: 10.1080/08897070209511496

Frangou, S. (2014). A systems neuroscience perspective of schizophrenia and bipolar disorder. *Schizophr. Bull.* 40, 523–531. doi: 10.1093/schbul/sbu017

Fuentes-Durá, I., Balanzá-Martínez, V., Ruiz-Ruiz, J. C., Martínez-Arán, A., Girón, M., Solé, B., et al. (2012). Neurocognitive training in patients with bipolar disorders—current status and perspectives. *Psychother. Psychosom.* 81, 250–252. doi: 10.1159/000335821

Goodwin, G. M., Martinez-Aran, A., Glahn, D. C., and Vieta, E. (2008). Cognitive impairment in bipolar disorder: neurodevelopment or neurodegeneration? An ECNP expert meeting report. *Eur. Neuropsychopharmacol.* 18, 787–793. doi: 10.1016/j.euroneuro.2008.07.005

Gorini, G., Harris, R. A., and Mayfield, R. D. (2014). Proteomic approaches and identification of novel therapeutic targets for alcoholism. *Neuropsychopharmacology* 39, 104–130. doi: 10.1038/npp.2013.182

Gupta, S., and Warner, J. (2008). Alcohol-related dementia: a 21st-century silent epidemic? *Br. J. Psychiatry* 193, 351–353. doi: 10.1192/bjp.bp.108.051425

Hermens, D. F., Scott, E. M., White, D., Lynch, M., Lagopoulos, J., Whitwell, B. G., et al. (2013). Frequent alcohol, nicotine or cannabis use is common in young persons presenting for mental healthcare: a cross-sectional study. *BMJ Open* 3:e002229. doi: 10.1136/bmjopen-2012-002229

Hoertel, N., de Maricourt, P., and Gorwood, P. (2013). Novel routes to bipolar disorder drug discovery. *Expert Opin. Drug Discov.* 8, 907–918. doi: 10.1517/17460441.2013.804057

Jaworski, F., Dubertret, C., Adès, J., and Gorwood, P. (2011). Presence of comorbid substance use disorder in bipolar patients worsens their social functioning to the level observed in patients with schizophrenia. *Psychiatry Res.* 185, 129–134. doi: 10.1016/j.psychres.2010.06.005

Johnson, C., Drgon, T., McMahon, F. J., and Uhl, G. R. (2009). Convergent genome wide association results for bipolar disorder and substance dependence. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* 150B, 182–190. doi: 10.1002/ajmg.b.30900

Jónsdóttir, H., Opjordsmoen, S., Birkenaes, A. B., Simonsen, C., Engh, J. A., and Ringen, P. A. (2013). Predictors of medication adherence in patients with schizophrenia and bipolar disorder. *Acta Psychiatr. Scand.* 127, 23–33. doi: 10.1111/j.1600-0447.2012.01911.x

Kapczinski, F., Dias, V. V., Kauer-Sant'Anna, M., Frey, B. N., Grassi-Oliveira, R., Colom, F., et al. (2009). Clinical implications of a staging model for bipolar disorders. *Expert Rev. Neurother.* 9, 957–966. doi: 10.1586/ern.09.31

Kapczinski, F., Magalhães, P. V., Balanzá-Martinez, V., Dias, V. V., Frangou, S., Gama, C. S., et al. (2014). Staging systems in bipolar disorder: an International Society for Bipolar Disorders Task Force Report. *Acta Psychiatr. Scand.* 130, 354–363. doi: 10.1111/acps.12305

Kessing, L. V., and Andersen, P. K. (2004). Does the risk of developing dementia increase with the number of episodes in patients with depressive disorder and in patients with bipolar disorder? *J. Neurol. Neurosurg. Psychiatr.* 75, 1662–1666. doi: 10.1136/jnnp.2003.031773

Kessler, R. C., Rubinow, D. R., Holmes, C., Abelson, J. M., and Zhao, S. (1997). The epidemiology of DSM-III-R bipolar I disorder in a general population survey. *Psychol. Med.* 27, 1079–1089. doi: 10.1017/S0033291797005333

Kurtz, M. M., and Gerraty, R. T. (2009). A meta-analytic investigation of neurocognitive deficits in bipolar illness: profile and effects of clinical state. *Neuropsychology* 23, 551–562. doi: 10.1037/a0016277

Langenbucher, J. W., and Chung, T. (1995). Onset and staging of DSM-IV alcohol dependence using mean age and survival-hazard methods. *J. Abnorm. Psychol.* 104, 346–354. doi: 10.1037/0021-843X.104.2.346

*Levy, B., Manove, E., and Weiss, R. D. (2012). Recovery of cognitive functioning in patients with co-occurring bipolar disorder and alcohol dependence during early remission from an acute mood episode. *Ann. Clin. Psychiatry* 24, 143–154.

*Levy, B., Monzani, B. A., Stephansky, M. R., and Weiss, R. D. (2008). Neurocognitive impairment in patients with co-occurring bipolar disorder and alcohol dependence upon discharge from inpatient care. *Psychiatry Res.* 161, 28–35. doi: 10.1016/j.psychres.2007.09.009

*Marshall, D. F., Walker, S. J., Ryan, K. A., Kamali, M., Saunders, E. F., Weldon, A. L., et al. (2012). Greater executive and visual memory dysfunction in comorbid bipolar disorder and substance use disorder. *Psychiatry Res.* 200, 252–257. doi: 10.1016/j.psychres.2012.06.013

Martinez-Aran, A., Scott, J., Colom, F., Torrent, C., Tabarés-Seisdedos, R., and Daban, C. (2009). Treatment nonadherence and neurocognitive impairment in bipolar disorder. *J. Clin. Psychiatry* 70, 1017–1023. doi: 10.4088/JCP.08m04408

Martínez-Arán, A., Torrent, C., Tabarés-Seisdedos, R., Salamero, M., Daban, C., Balanzá-Martínez, V., et al. (2008). Neurocognitive impairment in bipolar patients with and without history of psychosis. *J. Clin. Psychiatry* 69, 233–239. doi: 10.4088/JCP.v69n0209

Martino, D. J., Strejilevich, S. A., Scápola, M., Igoa, A., Marengo, E., Ais, E. D., et al. (2008). Heterogeneity in cognitive functioning among patients with bipolar disorder. *J. Affect. Disord.* 109, 149–156. doi: 10.1016/j.jad.2007.12.232

McElroy, S. L., Altshuler, L. L., Suppes, T., Keck, P. E. Jr., Frye, M. A., Denicoff, K. D., et al. (2001). Axis I psychiatric comorbidity and its relationship to historical illness variables in 288 patients with bipolar disorder. *Am. J. Psychiatry* 158, 420–426. doi: 10.1176/appi.ajp.158.3.420

McIntyre, R. S., Cha, D. S., Jerrell, J. M., Swardfager, W., Kim, R. D., Costa, L. G., et al. (2014). Advancing biomarker research: utilizing 'Big Data' approaches for the characterization and prevention of bipolar disorder. *Bipolar Disord.* 16, 531–547. doi: 10.1111/bdi.12162

Merikangas, K. R., Akiskal, H. S., Angst, J., Greenberg, P. E., Hirschfeld, R. M., Petukhova, M., et al. (2007). Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. *Arch. Gen. Psychiatry* 64, 543–552. doi: 10.1001/archpsyc.64.5.543

Mitchell, J. D., Brown, E. S., and Rush, A. J. (2007). Comorbid disorders in patients with bipolar disorder and concomitant substance dependence. *J. Affect. Disord.* 102, 281–287. doi: 10.1016/j.jad.2007.01.005

Momenan, R., Steckler, L. E., Saad, Z. S., van Rafelghem, S., Kerich, M. J., and Hommer, D. W. (2012). Effects of alcohol dependence on cortical thickness as determined by magnetic resonance imaging. *Psychiatry Res.* 204, 101–111. doi: 10.1016/j.pscychresns.2012.05.003

Nery, F. G., Hatch, J. P., Monkul, E. S., Matsuo, K., Zunta-Soares, G. B., Bowden, C. L., et al. (2013). Trait impulsivity is increased in bipolar disorder patients with comorbid alcohol use disorders. *Psychopathology* 46, 145–152. doi: 10.1159/000336730

Nery, F. G., Matsuo, K., Nicoletti, M. A., Monkul, E. S., Zunta-Soares, G. B., Hatch, J. P., et al. (2011). Association between prior alcohol use disorders and decreased prefrontal gray matter volumes in bipolar I disorder patients. *Neurosci. Lett.* 503, 136–140. doi: 10.1016/j.neulet.2011.08.026

Oquendo, M. A., Currier, D., Liu, S. M., Hasin, D. S., Grant, B. F., and Blanco, C. (2010). Increased risk for suicidal behavior in comorbid bipolar disorder and alcohol use disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). *J. Clin. Psychiatry* 71, 902–909. doi: 10.4088/JCP.09m05198gry

Pacchiarotti, I., Di Marzo, S., Colom, F., Sánchez-Moreno, J., and Vieta, E. (2009). Bipolar disorder preceded by substance abuse: a different phenotype with not so poor outcome? *World J. Biol. Psychiatry* 10, 209–216. doi: 10.1080/15622970701558488

Pettorruso, M., De Risio, L., Di Nicola, M., Martinotti, G., Conte, G., and Janiri, L. (2014). Allostasis as a conceptual framework linking bipolar disorder and addiction. *Front. Psychiatry* 5:173. doi: 10.3389/fpsyt.2014.00173

Post, R. M., and Kalivas, P. (2013). Bipolar disorder and substance misuse: pathological and therapeutic implications of their comorbidity and cross-sensitisation. *Br. J. Psychiatry* 202, 172–176. doi: 10.1192/bjp.bp.112.116855

Post, R. M., and Leverich, G. S. (2006). The role of psychosocial stress in the onset and progression of bipolar disorder and its comorbidities: the need for earlier and alternative modes of therapeutic intervention. *Dev. Psychopathol.* 18, 1181–1211. doi: 10.1017/S0954579406060573

Regier, D. A., Farmer, M. E., Rae, D. S., Locke, B. Z., Keith, S. J., Judd, L. L., et al. (1990). Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) Study. *JAMA* 264, 2511–2518. doi: 10.1001/jama.1990.03450190043026

Robinson, L. J., and Ferrier, I. N. (2006). Evolution of cognitive impairments in bipolar disorder: a systemic review of cross-sectional evidence. *Bipolar Disord.* 8, 103–116. doi: 10.1111/j.1399-5618.2006.00277.x

Rubio, J. M., Olfson, M., Villegas, L., Pérez-Fuentes, G., Wang, S., and Blanco, C. (2013). Quality of life following remission of mental disorders: findings from the National Epidemiologic Survey on Alcohol and Related Conditions. *J. Clin. Psychiatry* 74:e445–e450. doi: 10.4088/JCP.12m08269

Salloum, I. M., and Thase, M. E. (2000). Impact of substance abuse on the course and treatment of bipolar disorder. *Bipolar Disord.* 2, 269–280. doi: 10.1034/j.1399-5618.2000.20308.x

Salomon, J. A., Vos, T., Hogan, D. R., Gagnon, M., Naghavi, M., Mokdad, A., et al. (2013). Common values in assessing health outcomes from disease and injury: disability weights measurement study for the Global Burden of Disease Study 2010. *Lancet* 380, 2129–2143. doi: 10.1016/S0140-6736(12)61680-8

*Sanchez-Moreno, J., Martinez-Aran, A., Colom, F., Scott, J., Tabares-Seisdedos, R., Sugranyes, G., et al. (2009b). Neurocognitive dysfunctions in euthymic bipolar patients with and without prior history of alcohol use. *J. Clin. Psychiatry* 70, 1120–1127. doi: 10.4088/JCP.08m04302

Sanchez-Moreno, J., Martinez-Aran, A., Tabares-Seisdedos, R., Torrent, C., Vieta, E., and Ayuso-Mateos, J. L. (2009a). Functioning and disability in bipolar disorder: an extensive review. *Psychother. Psychosom.* 78, 285–297. doi: 10.1159/000228249

Sánchez-Morla, E. M., Barabash, A., Martínez-Vizcaíno, V., Tabarés-Seisdedos, R., Balanzá-Martínez, V., Cabranes-Díaz, J. A., et al. (2009). Comparative study of neurocognitive function in euthymic bipolar patients and stabilized schizophrenic patients. *Psychiatry Res.* 169, 220–228. doi: 10.1016/j.psychres.2008.06.032

Savitz, J., Solms, M., and Ramesar, R. (2005). Neuropsychological dysfunction in bipolar affective disorder: a critical opinion. *Bipolar Disord.* 7, 216–235. doi: 10.1111/j.1399-5618.2005.00203.x

Schoepf, D., and Heun, R. (2014). Bipolar disorder and comorbidity: increased prevalence and increased relevance of comorbidity for hospital-based mortality during a 12.5-year observation period in general hospital admissions. *J. Affect. Disord.* 169, 170–178. doi: 10.1016/j.jad.2014.08.025

Schulte, M. H., Cousijn, J., den Uyl, T. E., Goudriaan, A. E., van den Brink, W., Veltman, D. J., et al. (2014). Recovery of neurocognitive functions following sustained abstinence after substance dependence and implications for treatment. *Clin. Psychol. Rev.* 34, 531–550. doi: 10.1016/j.cpr.2014.08.002

Selva, G., Salazar, J., Balanzá-Martínez, V., Martínez-Arán, A., Rubio, C., Daban, C., et al. (2007). Bipolar I patients with and without a history of psychotic symptoms: do they differ in their cognitive functioning? *J. Psychiatr. Res.* 41, 265–272. doi: 10.1016/j.jpsychires.2006.03.007

*Shan, C., Lee, S. Y., Chang, Y. H., Wu, J. Y., Chen, S. L., Chen, S. H., et al. (2011). Neuropsychological functions in Han Chinese patients in Taiwan with bipolar II disorder comorbid and not comorbid with alcohol abuse/alcohol dependence disorder. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 35, 131–136. doi: 10.1016/j.pnpbp.2010.10.004

Solé, B., Bonnin, C. M., Torrent, C., Balanzá-Martínez, V., Tabarés-Seisdedos, R., Popovic, D., et al. (2012). Neurocognitive impairment and psychosocial functioning in bipolar II disorder. *Acta Psychiatr. Scand.* 125, 309–317. doi: 10.1111/j.1600-0447.2011.01759.x

Spanagel, R., Durstewitz, D., Hansson, A., Heinz, A., Kiefer, F., Köhr, G., et al. (2013). A systems medicine research approach for studying alcohol addiction. *Addict. Biol.* 18, 883–896. doi: 10.1111/adb.12109

Stavro, K., Pelletier, J., and Potvin, S. (2013). Widespread and sustained cognitive deficits in alcoholism: a meta-analysis. *Addict. Biol.* 18, 203–213. doi: 10.1111/j.1369-1600.2011.00418.x

Svanberg, J., and Evans, J. J. (2013). Neuropsychological rehabilitation in alcohol-related brain damage: a systematic review. *Alcohol Alcohol* 48, 704–711. doi: 10.1093/alcalc/agt131

Swann, A. C. (2010). The strong relationship between bipolar and substance use disorder. *Ann. N.Y. Acad. Sci.* 1187, 276–293. doi: 10.1111/j.1749-6632.2009.05146.x

Swann, A. C., Lijffijt, M., Lane, S. D., Steinberg, J. L., and Moeller, F. G. (2009). Increased trait-like impulsivity and course of illness in bipolar disorder. *Bipolar Disord.* 11, 280–288. doi: 10.1111/j.1399-5618.2009.00678.x

Tabarés-Seisdedos, R., Balanzá-Martínez, V., Sánchez-Moreno, J., Martínez-Arán, A., Salazar-Fraile, J., Selva-Vera, G., et al. (2008). Neurocognitive and clinical predictors of functional outcome in patients with schizophrenia and bipolar I disorder at one-year follow-up. *J. Affect. Disord.* 109, 286–299. doi: 10.1016/j.jad.2007.12.234

Tolliver, B. K., and Hartwell, K. J. (2012). Implications and strategies for clinical management of co-occurring substance use in bipolar disorder. *Psychiatr. Ann.* 42, 190–197. doi: 10.3928/00485713-20120507-07

Torrent, C., Del Mar Bonnin, C., Martínez-Arán, A., Valle, J., Amann, B. L., González-Pinto, A., et al. (2013). Efficacy of functional remediation in bipolar disorder: a multicenter randomized controlled study. *Am. J. Psychiatry* 170, 852–859. doi: 10.1176/appi.ajp.2012.12070971

Torres, I. J., Boudreau, V. G., and Yatham, L. N. (2007). Neuropsychological functioning in euthymic bipolar disorder: a meta-analysis. *Acta Psychiatr. Scand. Suppl.* 434, 17–26. doi: 10.1111/j.1600-0447.2007.01055

Torres, I. J., Kozicky, J., Popuri, S., Bond, D. J., Honer, W. G., Lam, R. W., et al. (2014). 12-month longitudinal cognitive functioning in patients recently diagnosed with bipolar disorder. *Bipolar Disord.* 16, 159–171. doi: 10.1111/bdi.12154

*van der Werf-Eldering, M. J., Burger, H., Holthausen, E. A., Aleman, A., and Nolen, W. A. (2010). Cognitive functioning in patients with bipolar disorder: association with depressive symptoms and alcohol use. *PLoS ONE* 5:e13032. doi: 10.1371/journal.pone.0013032

*van Gorp, W. G., Altshuler, L., Theberge, D. C., Wilkins, J., and Dixon, W. (1998). Cognitive impairment in euthymic bipolar patients with and without prior alcohol dependence. A preliminary study. *Arch. Gen. Psychiatry* 55, 41–46. doi: 10.1001/archpsyc.55.1.41

Vieta, E., Azorin, J. M., Bauer, M., Frangou, S., Perugi, G., Martinez, G., et al. (2012). Psychiatrists' perceptions of potential reasons for non- and partial adherence to medication: results of a survey in bipolar disorder from eight European countries. *J. Affect. Disord.* 143, 125–130. doi: 10.1016/j.jad.2012.05.041

Wingo, A. P., Harvey, P. D., and Baldessarini, R. J. (2009). Neurocognitive impairment in bipolar disorder patients: functional implications. *Bipolar Disord.* 11, 113–125. doi: 10.1111/j.1399-5618.2009.00665.x

Wollenweber, F. A., Halfter, S., Brügmann, E., Weinberg, C., Cieslik, E. C., Müller, V. I., et al. (2014). Subtle cognitive deficits in severe alcohol addicts—do they show a specific profile? *J. Neuropsychol.* 8, 147–153. doi: 10.1111/jnp.12001

Wu, K. Y., Chang, C. M., Liang, H. Y., Wu, C. S., Wu, E. C. H., Chen, C. H., et al. (2013). Increased risk of developing dementia in patients with bipolar disorder: a nested matched case–control study. *Bipolar Disord.* 15, 787–794. doi: 10.1111/bdi.12116

Conflict of Interest Statement: Dr. Balanzá-Martínez has received grants and served as consultant, advisor or CME speaker during the last four years for the following entities: Almirall; Angelini; AstraZeneca; Bristol-Myers-Squibb; Janssen; Juste; Lundbeck; Otsuka; Spanish Ministry of Science and Innovation (CIBERSAM); and Fundación Alicia Koplowitz. Dr. Crespo-Facorro declares that he has no conflict with the contents of this paper. Dr. González-Pinto has received grants from or served as consultant, adviser, or CME speaker for Almirall, AstraZeneca, Bristol-Myers Squibb, Cephalon, Eli Lilly, GlaxoSmithKline, Janssen-Cilag, Lundbeck, Merck, Novartis, Otsuka, Pfizer, Sanofi- Aventis, Schering-Plough, and the Spanish Ministry of Science and Innovation (CIBERSAM). Dr. Vieta has received grants, CME-related honoraria, or consulting fees from Alexza, Almirall, AstraZeneca, Bristol-Myers Squibb, Cephalon, Eli Lilly, Ferrer, Forest Research Institute, Gedeon Richter, GlaxoSmith-Kline, Janssen, Janssen-Cilag, Jazz, Johnson and Johnson, Lundbeck, Merck, Novartis, Organon, Otsuka, Pfizer, Pierre-Fabre, Qualigen, Roche, Sanofi-Aventis, Schering-Plough, Servier, Shire, Solvay, Takeda, Teva, CIBERSAM, the Seventh European Framework Programme (ENBREC), the Stanley Medical Research Institute, United Biosource Corporation, and Wyeth.

*Papers selected in the systematic review.