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Review article

Neurocognitive functioning in the premorbid stage and in the first episode of bipolar disorder: A systematic review

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ABSTRACT

It is well known that patients with bipolar disorder (BD) have cognitive impairments even during periods of euthymia. However, to date it remains unclear the moment when these deficits onset. Therefore, the aim of this study was to review the evidence focusing on the cognitive status of patients with BD in their premorbid stage and in their first episode. An extensive search was conducted through the online databases Pubmed/PsychInfo, covering the period between 1980 and 2014. A total of 23 studies were selected for the review (nine studies explored premorbid stage of people who lately develop BD and 14 examined first-episodes in bipolar patients). There is evidence that general intelligence is not impaired in the premorbid stage. Impairments in verbal memory, attention, and executive functions tend to be present during and after the first episode. Preliminary evidence suggests that these deficits in specific cognitive domains might precede the onset of illness.

Contents

1. Introduction

Over the last two decades, a growing body of evidence has suggested that euthymic patients with bipolar disorder (BD) have impairments in verbal memory, attention, and executive functions compared with healthy controls, with medium–large effect sizes in most studies (Robinson et al., 2006; Torres et al., 2007; Bora et al., 2009; Mann-Wrobel et al., 2011) and somewhat less in other (Bourne et al., 2013). Cognitive deficits in BD are present in different subtypes of the disorder (Martino et al., 2011a; Bora et al., 2011) and may extend beyond traditional neurocognitive domains (Martino et al., 2011b; Samamé et al., 2012). Likewise, the association between cognitive deficits and functional outcome has been consistently reported both in cross-sectional (Zubieta et al., 2001; Dickerson et al., 2004; Martinez-Arán et al., 2004) and longitudinal

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(Jaeger et al., 2007; Tabarés-Seisdedos et al., 2008; Martino et al., 2009) studies.

Despite the advance in the field of neurocognition, to date it is not clear when the cognitive impairments onset in patients with BD. Some recent reviews have suggested that patients with BD show relatively intact cognitive status in the premorbid stage, throughout childhood and adolescence, and that it is just when symptoms of illness arise that neurocognitive functioning deteriorates (Kumar and Frangou., 2010; Lewandowski et al., 2011; Trotta et al., 2014). This perspective is in accordance, regarding the neurocognitive performance in the premorbid stage, with the notion of illness progression and staging introduced in BD (Berk., 2009; Kapczinski et al., 2009; Post et al., 2012; Kapczinski et al., 2014). The model of staging proposes a progression from latent (at-risk) to more severe and refractory presentations associated with the cumulative effects of illness episodes, drugs abuse, life stress, and inherited vulnerability (Kapczinski et al., 2009). Specifically from a neurocognitive point of view, staging models suggest no cognitive impairments in the premorbid stage or even in patients with well-defined periods of euthymia without overt psychiatric symptoms, to progressive cognitive impairments in further stages (Kapczinski et al., 2009).

Data about intact premorbid cognitive functioning in patients with BD contrast, however, with findings from neurocognitive studies in healthy first-degree relatives of affected subjects. Arts et al. (2008) conducted a meta-analysis and reported that, compared with 692 healthy controls, the 336 first-degree relatives of probands with BD had impairments in executive functions and verbal memory with small effect sizes. In this study, the performance of first-degree relatives was intermediate between the ones of healthy controls and patients with BD (Arts et al., 2008). Similarly, Bora et al. (2009) in another meta-analysis found that 443 first-degree relatives of patients with BD had impairments in response inhibition, set shifting, executive function, verbal memory, and sustained attention with small to medium effect sizes. Therefore, the fact that patients with BD have a preserved premorbid cognitive functioning as suggested, while healthy first-degree relatives of bipolar subjects do not, is somewhat contradictory. It has been recently pointed out that this contradiction could be due to sample selection bias, medication, drug use, cognitive decline prior to the first episode, or other confounding factors (Arango et al., 2014).

These controversial results warrant further research in this field. Clarification of the onset of neurocognitive deficits is relevant to a better clinical description of the disorder, to identifying similarities and differences with other neuropsychiatric disorders, and to contribute to understanding pathophysiological processes underlying this illness. Accordingly, the aim of this study was to review the evidence gathered in recent years focusing on the cognitive status of patients with BD in their premorbid stage and in their first episode, in order to gain some insight into the onset of neurocognitive impairments in BD.

2. Methods

Articles were retrieved from the online databases Pubmed/PsychInfo using combinations of the following keywords: bipolar, cognit*, neuropsychol*, neurocogniti*, intelligence, attention, language, memory, executive, premorbid, high-risk, first-episode, and longitudinal. The reference lists of the studies identified for inclusion were also reviewed for additional relevant reports.

Reports were considered for this review if they meet the following inclusion criteria: (I) were published in a peer-reviewed English language journal between January 1980 and May 2014 (1980 was selected as a date limit considering that the publication of DSM-III enables to include studies with more precise diagnostic criteria); (II) included a patient group in a premorbid stage diagnosed during a follow-up period as BD, or a patient group in their first psychotic/manic/mixed episode diagnosed as BD (thus, studies of patients with recent onset psychosis, which are not necessary in the first episode of illness, were not included); (III) diagnosis of BD was ascertained according to standardized diagnostic criteria (RDC, DSM-III, DSM-IV, ICD-10, etc.); (IV) included a control group; and (V) included at least one traditional neurocognitive measure (social cognition measures or experimental paradigms were not included). Therefore, studies that used only measures of premorbid IQ, such as vocabulary or word reading task, in samples of (post-onset) patients with BD were not included. Likewise, studies that included only proxies of neurocognitive functioning such as educational test scores or school performance or overall measures of premorbid functioning were not included. Finally, studies on the same patient sample were only included if these reported different neurocognitive measures or results.

3. Results

The electronic search provided 597 publications for analysis. On the basis of title and abstract, 533 studies were excluded. A total of 64 studies were considered potentially relevant and full text was assessed manually. Of these, 37 did not satisfy one or more of the inclusion criteria and were excluded. Five studies were also excluded as they were based on the same sample used in other studies (Zanelli et al., 2013; Kozicky et al., 2013, 2014; Bücker et al., 2014; Torres et al., 2014). A total of 23 studies were selected for the review (9 studies explored premorbid stage and 14 examined first-episodes including 617 and 383 bipolar patients respectively). The key features of these studies are summarized in Tables 1 and 2.

3.1. Neurocognitive functioning in the premorbid stage

Different methodologies were employed to appraise neurocognitive functioning in the premorbid stage, such as conscript studies and cohort studies based either on general population samples or on clinical/genetical high-risk samples for BD.

Conscript studies are based on samples of young adult males that require certain neurocognitive tests prior to enlisting in the military service. Typically, these large studies use general measures of neurocognitive functioning, such as IQ, rather than tasks assessing specific neurocognitive domains. Reichenberg et al. (2002) used the Israeli Draft Board Registry to examine an unselected population of 16- to 17-year-old males between 1985 and 1991. A combined score of a modified Otis-type verbal intelligence test, a revised version of the “similarities” subtest of the Wechsler Adult Intelligence Scale, and a modified version of Raven's Progressive Matrices was used as a measure of intellectual functioning. These data were merged with the National Psychiatric Hospitalization Case Registry, which contains diagnoses for all patients with psychiatric hospitalizations in Israel. Subjects with schizophrenia performed significantly worse on these measures than those with a nonpsychotic BD, who did not differ significantly from the comparison subjects on any measure. Similarly, Zammit et al. (2004) studied a cohort of 50,087 18–20 year-old males conscripted into the Swedish Army between 1969 and 1970. Tests of verbal and visuospatial abilities, general and mechanical knowledge were aggregated into an overall standardized general intelligence score. The Swedish National Hospital Discharge Register was used to identify hospital admissions during a 27-year follow-up period. Lower premorbid IQ was associated with increased risk of schizophrenia, severe depression, and nonaffective psychosis. However, patients with BD had no differences in overall premorbid IQ or in subtests with respect to healthy controls. Tiihonen et al. (2005) examined a cohort of 195,019 healthy male subjects conscripted into the Finnish Defense Forces during 1982–1987 (mean age, 19.9 years) with verbal, arithmetic, and visuospatial reasoning tests. The Finnish Hospital Discharge Register (mean follow-up time, 7.1 years) was used to identify conscripts later diagnosed with bipolar disorder, schizophrenia, or other psychoses. Poor performance on the visuospatial reasoning test was associated with higher risks for all three disorders, while BD was

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Table 1
Summary of studies assessing neurocognitive functioning in premorbid stage on bipolar disorder.

Primary study	Age at baseline	Follow-up (years)	Original sample/Diagnosis at follow-up	Cognitive measures	Main results
Conscript studies					
Reichenberg et al., 2002	16–17	11	Unselected population of Israeli adolescents between 1985–1991/Hospitalized for non-psychotic BD ($n=68$), SCH-Aff ($n=31$), or SCH ($n=536$).	Otis verbal intelligence[a] Raven's Progressive Matrices[a] Similarities WAIS[a] Intellectual functioning	SCH < BD = HC in all these measures
Zammit et al., 2004	18–20	27	50,087 male subjects conscripted during 1969–1970/Hospitalized for BD ($n=108$), SCH ($n=362$), severe UD ($n=113$), and non-affective psychosis ($n=223$)	Verbal IQVisuospatial abilityGeneral knowledge and intelligenceMechanical knowledge	SCH, severe UD, and non-affective psychosis < BD = HC on premorbid performance.
Tiihonen et al., 2005	19.9	7.1	195,019 healthy male subjects conscripted during 1982–1987/Hospitalized for BD ($n=100$), SCH ($n=621$), and other psychoses ($n=527$)	Finnish Defense Forces Basic Ability Test	BD = SCH = other psychosis < HC on visuospatial reasoning. BD > HC in arithmetic reasoning.
Sørensen et al., 2012	19.5	13–34	Historical all male sample born between 1950–1961/Hospitalized for BD ($n=294$), and UD ($n=1434$)	Børge Priens Prøve	UD = BD < HC = BD on premorbid IQ.
Birth cohort studies					
Cannon et al., 2002	3	15–23	A 1-year birth cohort of 1037 children/SCH spectrum ($n=36$), mania ($n=20$), anxiety/UD ($n=278$)	Peabody Picture Vocabulary test, Stanford–Binet Intelligence Scale, and WISC-R	SCHspectrum < mania = anxiety/depression = HC on premorbid intelligence
Koenen et al., 2008	7	25	A 1-year birth cohort of 1037 children/25 /SCH spectrum ($n=35$), mania ($n=8$), anxiety/UD ($n=353$), substance dependence ($n=154$)	WISC-R	SCHspectrum = anxiety/depression < HC = substance dependence on premorbid intelligence. Mania > HC on premorbid intelligence.
High risk studies					
Meyer et al., 2004	11–19	23	102 offspring (72 with high risk for BD/UD)/BD ($n=9$), and UD ($n=22$)	WISC-R WCST, TMT-A, TMT-B	UD = HC > BD = HC on premorbid IQ BD = UD = HC on TMT-A and TMT-B UD = HC > BD on performance in WCST
Olvet et al., 2010	15–17	NR	147 CHR psychosis/SCH-Spectrum ($n=24$), BD ($n=8$)	WRAT-3 Global Neurocognitive Z-score	BD = SCH-Spectrum = HC on premorbid IQ BD = HC > SCH = BD on Global Z-score
Ratheesh et al., 2013	20	4–13	416 CHR psychosis/BD ($n=5$–10)	WAIS-R / WASI RAVLT Picture Completion TMT-A / TMT-B COWAT	BD < HC on premorbid IQ/Full Scale IQ BD < < HC Picture Completion BD < HC TMT-A/TMT- B

BD: Bipolar disorder; SCH-Aff: Schizoaffective; SCH: Schizophrenia; UD: unipolar depression; CHR: Clinical High Risk; HC: healthy controls; NR: no reported; WAIS: Wechsler Adult Intelligence Scale; WISC-R: Weschler Intelligence Scale for Children-Revised; WCST: Wisconsin Card Sorting Test; TMT-A: Trail Making Test part A; TMT-B: Trail Making Test part B; WRAT-3: Wide Range Achievement Test; WASI: Wechsler Abbreviated Scale of Intelligence;

[a] Modified version.

also related with an increased performance on the arithmetic subtest. Finally, Sørensen et al. (2012) examined a historical all male sample born between 1950 and 1961, and identified those hospitalized with a diagnosis of BD or unipolar disorder as well as healthy controls by Danish Psychiatric Central Research Register until 2004. Premorbid IQ was assessed by composite measure four subtests (letter matrices, verbal analogies, number series, and geometric figures) as a part of the draft board previous to conscription (mean age 19.5 years). Patients with unipolar depression had lower premorbid IQ than healthy controls, while patients with BD had no significant differences either with unipolar patients or with healthy controls (Sørensen et al., 2012).

Another possible approach consists in the study of large birth cohort from the general population longitudinally. To our knowledge, only one birth cohort explored the neurocognitive functioning of patients who later were diagnosed as BD (Cannon et al., 2002; Koenen et al., 2009). The Dunedin Multidisciplinary Health and Development Study was a longitudinal investigation of a complete cohort of children ($n=1037$) born during a 1-year period in 1972–1973. Neurocognitive functioning was assessed with the Weschler Intelligence Scale for Children-Revised at ages 3–11. Initially, impairments in cognitive development were present only among children later diagnosed at age 26 with the Diagnostic Interview Schedule as having schizofreniform disorder, while mania and anxiety/depression groups did not differ significantly from controls (Cannon et al., 2002). However, in a later follow-up at age 32, a high IQ in childhood was associated with increased risk for mania in a small sample ($n=8$) (Koenen et al., 2009).

A third line of investigations focused on the evaluation of neurocognitive functioning of people with high risk to affective/psychotic disorder who is later diagnosed as BD. Meyer et al. (2004) used data from a 23-year longitudinal prospective study of offspring of mothers with BD, unipolar depression, or no history of psychiatric illness. Offspring which were later diagnosed as BD ($n=9$) had lower performance than healthy controls on measures of executive functions with effect sizes in the moderate–large range (ES range = 0.58–1.34) at age 11–19 although they had comparable full-scale IQ (Meyer et al., 2004). Olvet et al. (2010)

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Table 2
Summary of studies assessing neurocognitive functioning in first episode on bipolar disorder.

Primary study	Sample[a]	Age of BD	Clinical state of BD patients: mean (S. D.) or median (range)	Cognitive measures	Main results
Payá et al., 2013	BD (n=23), SCH (n=46), HC (n=91)	16.0	No specifically reported/No euthymic	Vocabulary subtest from WAIS or WISC-R	BD=SCH < HC on premorbid IQ (ES=1.15).
Zabala et al., 2010	BD (n=19), SCH (n=36), other psychosis (n=52), HC (n=98)	15.7	PANSS positive=14.89 (6.79), PANSS negative=14.47 (5.02), PANSS general=34.53 (9.54)	WAIS Digit Span/ Number-letter sequencing CVLT TMT-A/Stroop/CPT TMT-B/WCST/ COWAT/FAS	BD=SCH=other psychosis < HC on overall measures of attention, verbal and working memory, and executive functions.
Barret et al., 2009	BD (n=32), SCH (n=46), HC (n=67)	36.7	PANSS positive=17.39 (5.51), PANSS negative=9.81 (3.25), PANSS mania=6.09 (1.67), BDI=9.07 (10.83)	WASI/NART WAIS Digit Span/ Memory Scale Corsi Block-tapping Test Rey Osterrieth Complex Figure Test Hayling and Brixton Tests/ COWAT	BD < HC on premorbid IQ (ES=0.42). BD < HC on current IQ (ES=0.52). BD < HC on working memory (ES=0.50), verbal (ES=0.71) and visual memory (ES=1.04), verbal response inhibition (ES=0.62) and language functioning (ES=0.98).
Zanelli et al., 2010	BD (n=37), psychotic UD (n=39), SCH (n=65), other psychosis (n=46), HC (n=177)	26.0 (male) 30.9 (female)	No specifically reported/No euthymic	NART/WAIS RAVLT/Wechsler Memory Scale TMT-A/WAIS Digit symbol TMT-B/ Letter-Number Span Test /Raven´s Matrices FAS / Category Fluency	BD=HC on premorbid and current IQ. BD < HC on verbal memory (ES=0.60) and category fluency (ES=0.75). SCH < HC on all measures.
Hirayasu et al., 2000	BD (n=24), SCH (n=20), HC (n=22)	23.6	No specifically reported / No euthymic	Information subtest from WAIS WAIS Digit Span	BD < HC on information (ES=0.65), attention (ES=0.63), and working memory (ES=0.71).
Ayres et al., 2006	BD (n=41), UD (n=31), SCH (n=98), HC (n=383)	33.5	No euthymic/BPRS=36.2 (11.7)	WAIS Digit Span COWAT	BD < HC on working memory (ES=0.43).
Fleck et al., 2008	BD (n=21) , HC (n=48)	25.7	YMRS=21.7 (11.8), HDRS=16.0 (5.7)	NART WCST	BD=HC on premorbid IQ. BD < HC on executive functions (ES=0.59–0.65).
Gruber et al., 2008	BD (n=26) , HC (n=20)	24.4	No specifically reported/No euthymic	Vocabulary subtest from WAIS Stroop/TMT-A/ TMT-BWCST/ COWAT/FAS	BD=HC on premorbid IQ. BD < HC on executive functions (ES range=0.60–1.07).
Hill et al., 2009	BD (n=22), psychotic UD (n=21), SCH (n=30), HC (n=41)	22.6	PANSS positive=23.48 (4.96), PANSS negative=12.62 (5.41), HDRS=29.14 (8.62)	WRAT-III Reading CVLT WAIS Digit Span/ TMT-A/CPT TMT-B/COWAT/ Cogtest	HC > SCH in all measures. BD intermediate performance between HC and SCH (ES range=0.44–0.79)
Hellvin et al., 2012	BD (n=34), HC (n=110)	31.2	PANSS positive=11.6 (7–27), PANSS negative=9.6 (7–20), YMRS=2 (0–28), IDS-C=14 (0–39)	NART CVLT/WAIS Memory Scale WAIS Digit Span/ Bergen n-back/ Number-letter sequencing WCST/Verbal Fluency Test/Colo-Word Interference Test WAIS Digit Symbol/ Grooved Pegboard	BD=HC on premorbid IQ. BD < HC on measures of verbal memory (ES=0.65), attention (ES=0.63), psychomotor speed (ES=1.01), working memory (ES=0.59), and executive functions (ES=0.78).
Lebowitz et al., 2001	BD (n=19), HC (n=30)	27.4	YMRS=16.6 (9.1), HDRS=15.5 (7.9)	NART FAS/COWAT	BD=HC on premorbid IQ. BD=HC on verbal fluency.
Nehra et al., 2006	BD (n=16), HC (n=20)	28.4	YMRS=1.44 (1.26), HDRS=1.37 (1.20)	BSB-R WAIS Memory Scale WCST/TMT-A and B/ COWAT/FAS Bender Visual Motor Gestalt Test	BD < HC on executive function (ES range=1.36–1.93), sustained attention (ES=1.43), perceptuomotor function (ES=1.88) and IQ (ES=1.25).
	BD (n=45), HC (n=25)	22.2			BD=HC on premorbid IQ and attention.

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Table 2 (*continued*)

Primary study	Sample[a]	Age of BD	Clinical state of BD patients: mean (S. D.) or median (range)	Cognitive measures	Main results
Torres et al., 2010			PANSS positive=7.8 (1.6), YMRS=1.8 (3.7), HDRS=4.3 (5.1)	NART/Kaufman Brief Intelligence CVLT TMT-A/Stroop /CANTAB TMT-B/ Number-letter sequencing	BD < HC on executive functions (ES=0.66), working memory (ES=0.78), and visual reasoning (ES=0.64).
López-Jaramillo et al., 2010	BD (*n*=24), HC (*n*=66)	37.0	YMRS=1.21 (1.50), HDRS=1.13 (1.15)	WAIS A Cancellation Test/TMT-A and B/Stroop/ WAIS Digit symbol WAIS Memory Scale/Digit Span WCST/Verbal Fluency Continuous Visual Execution Test	BD < HC on working memory (ES=0.71).

BD: bipolar disorder; SCH: Schizophrenia; UD: unipolar depression; HC: healthy controls; NR: No reported; PANSS: Positive and Negative Syndrome Scale; BDI: Beck Depression Inventory; YMRS: Young Mania Rating Scale; HDRS: Hamilton Depression Rating Scale; BPRS: Brief Psychiatric Rating Scale; IDS-C: Inventory of Depressive Symptoms–Clinician rated; WAIS: Wechsler Adult Intelligence Scale; WISC-R: Weschler Intelligence Scale for Children-Revised; WCST: Wisconsin Card Sorting Test; TMT-A: Trail Making Test part A; TMT-B: Trail Making Test part B; COWAT: Control Oral Word Association test; FAS: Verbal Fluency test; CVLT: California Verbal Learning test; WASI: Wechsler Abbreviated Scale of Intelligence; NART: National Adult Reading Test; RAVLT: Rey Auditory Verbal Learning Test; WRAT: Wide Range Achievement Test; BSB-R: Bhatia's Battery of Performance Tests of Intelligence; ES=effect size.

[a] Only patients with BD during first episodes were considered.

examined subjects who were initially identified as clinical high-risk (by the presence of attenuated positive symptoms) for schizophrenia during the prodromal phase of the illness and followed them prospectively. Neurocognitive functioning was assessed with an overall measure (global neurocognitive score) derived for several neurocognitive tasks assessing verbal memory, attention, psychomotor speed, and executive functions. Patients who later were diagnosed with BD did not differ from those with schizophrenia or healthy controls in terms of premorbid IQ and global neurocognitive score (Olvet et al., 2010). Similarly, Ratheesh et al. (2013) followed-up 4–13 years a cohort of 416 young people who were at ultra-high risk for psychosis. Baseline neurocognitive functioning showed that people who after were diagnosed as BD (*n*=5–10) had lower performance than healthy controls on measures of global intelligence, visuospatial ability, and executive functions with large effect sizes for all measures (ES range=1.35–1.56) (Ratheesh et al., 2013).

3.2. Neurocognitive functioning in first episodes

Studies assessing neurocognitive functioning in first episodes includes both patients with their first psychotic or manic/mixed episodes that are diagnosed prospectively as BD. Likewise, studies of first episodes may be separated into those of symptomatic patients and those of euthymic patients.

Two studies reported results from a sample of patients between 7–17 years with a first psychotic episode from a longitudinal multicenter study (Zabala et al., 2010, Payá et al., 2013). In this sample, patients not entirely euthymic had lower premorbid IQ (Payá et al., 2013) as well as poorer performance on measures of verbal memory, attention, working memory, and executive functions (Zabala et al., 2010) in comparison to healthy controls. Moreover, authors found no differences between patients with BD and those with first psychotic episode of schizophrenia for these measures. Other studies explored neurocognitive functioning in samples of adult symptomatic patients experiencing their first psychotic episode. In the study by Barret et al. (2009) there were lower performances in BD compared with healthy controls on measures of premorbid and current IQ with moderate effect sizes. Likewise, dysfunctions in working memory, verbal and visual memory, executive set shifting, verbal inhibition, and language functioning were present in patients, with moderate–large effect. This profile of cognitive impairments was comparable to that of patients with 'preserved IQ' schizophrenia. By contrast, Zanelli et al. (2010) reported that BD patients exhibited similar premorbid and current IQ and only lower performance of moderate effect in verbal memory and categorical fluency compared with that of healthy controls. This profile differed from that of patients with schizophrenia, who showed cognitive impairments in almost all cognitive domains assessed (Zanelli et al., 2010). Similarly, Hirayasu et al. (2000) reported a lower performance in BD compared with healthy subjects in measures of general information, attention and working memory. Finally, Ayres et al. (2007) found that BD patients underperformed in a measure of working memory while patients with schizophrenia also have dysfunction in a verbal fluency task.

On the other hand, another group of studies explored neurocognitive functioning in symptomatic patients experiencing their first manic/mixed episode independently of the presence of psychotic symptoms. Overall, these studies consistently showed impairments in different measures of executive functioning with moderate–large patient-control effects (Fleck et al., 2008; Gruber et al., 2008; Hill et al., 2009; Hellvin et al., 2012). Similarly, the two studies that included tasks of verbal and working memory, and attention/processing speed found that BD patients had lower performance than healthy subjects with moderate effect sizes for almost all measures (Hill et al., 2009; Hellvin et al., 2012). In contrast, Lebowitz et al. (2001) did not found differences between BD patients during their first manic episode and healthy controls in terms of verbal fluency.

Finally, a few studies included euthymic patients after recovery from their first manic episode. In the study by Nehra et al. (2006) a small sample of euthymic BD patients after their first manic episodes showed impairments in IQ, executive functions, verbal memory, and attention with large effect sizes for all measures. Likewise, Torres et al. (2010) reported that patients with BD had a

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comparable performance in premorbid IQ and attention relative to controls, while finding impairments of moderate effect in measures of executive functions, working memory, and visual reasoning. In addition, López-Jaramillo et al. (2010) found that patients with BD performed worse than controls only on a measure of working memory with moderate effect size, without differences between groups in IQ, verbal memory, attention/processing speed, and executive functions.

4. Discussion

There is a paucity of studies that explored the neurocognitive functioning of patients with BD in the premorbid stage and in the first episode of the disorder. In addition, several considerations must be taken into account to interpret the results of this review. First, conscript studies (Reichenberg et al., 2002; Zammit et al., 2004; Tiihonen et al., 2005; Sørensen et al., 2012) used National Registers to ascertain diagnosis during hospital admissions, so there is a risk of selection bias towards more severe forms of the disorder requiring hospitalization in these studies. The bias is avoided in birth cohort studies because they longitudinally evaluate the diagnosis through standardized instruments in the still living cohort members (Cannon et al., 2002; Koenen et al, 2009). Second, studies of neurocognitive functioning based on high risk of psychosis samples (Olvet et al., 2010; Ratheesh et al., 2013) could confuse the premorbid stage, which involves the absence of illness, with prodromal symptoms of the first episode or symptoms of comorbid conditions such as schizotypal traits. Therefore, samples of high risk of BD (offspring of probands with BD) (Meyer et al., 2004) could be preferred over those samples based on high risk of psychosis to assess neurocognitive functioning in the premorbid stage of people later diagnosed as BD. Third, several research reports of first psychotic/manic/mixed episode of BD included patients not always in euthymic states, which is relevant due to the fact that neurocognitive deficits are known to worsen during mood episodes (Kurtz and Gerraty, 2009). Therefore, the studies that employ symptomatic or not entirely euthymic patients do not allow for the distinction between trait or state cognitive deficits. By contrast, there are few studies of first episode of BD that used more conservative criteria of euthymia (Nehra et al., 2006; Torres et al., 2010; López-Jaramillo et al., 2010). Even in some of these studies certain key variables, such as age or IQ, were not properly matched between patient-control groups making it difficult to attribute cognitive deficits to BD itself (Nehra et al., 2006).

Given these considerations, and in order to explore the onset of neurocognitive impairments reported in patients with BD, one of the focuses of this review were findings in patients with first episodes. Most studies in not entirely euthymic patients experienced their first psychotic/manic/mixed episode reported a profuse profile of neurocognitive impairments compromising domains of working memory/executive functions, verbal memory, and attention/processing speed. Among the studies that used more conservative criteria of euthymia there were impairments only in a measure of working memory in the one study (López-Jaramillo et al., 2010), while there were more extensive impairments including domains of executive functions, attention, verbal memory, and visuospatial abilities in others (Nehra et al., 2006; Torres et al., 2010). These results agree with those of a recent meta-analysis of the neurocognitive functioning in first episode BD that found medium to large effect size deficits for executive functions, and attention/psychomotor speed, whereas small to medium decrements were found for verbal learning and memory (Lee et al., 2014). Together, these results suggest that cognitive impairments are present during the first episode of the disorder and after its remission. However, these cognitive deficits may precede the onset of BD or develop together with the emergence of affective symptoms during the first episode of the disorder. Then, a second focus of this review was the neurocognitive functioning of BD patients in the premorbid stage.

With the exception of one study that reported that a high IQ was associated with increased risk for mania (Koenen et al., 2009) and other that showed that both poor performance on the visuospatial reasoning and increased performance on the arithmetic subtest were associated with BD (Tiihonen et al., 2005), most studies found that people who later were diagnosed as BD had a level of general intelligence in the premorbid stage comparable to that of healthy controls (Reichenberg et al., 2002; Cannon et al., 2002; Zammit et al., 2004; Sørensen et al., 2012). These results are in accordance with all meta-analyses in adult patients with BD, which showed no differences with controls in the level of premorbid IQ measured with vocabulary or word reading tasks (Robinson et al., 2006; Torres et al., 2007; Arts et al., 2008; Bora et al., 2009; Mann-Wrobel et al., 2011). Moreover, the same results of preserved performance in measures of premorbid or current IQ were obtained from meta-analyses of first-degree relatives of probands with BD (Arts et al., 2008; Bora et al., 2009). Overall, these data suggest that general intelligence tends to be preserved in premorbid stage of patients with BD. However, it does not necessarily mean that patients with BD have a preserved neurocognitive functioning before their illness onset, since it may be that only specific cognitive domains (i.e. executive functions or verbal memory), which are not reflected in general intelligence or IQ measures, are impaired at premorbid stage. In fact, this is the case in adult patients with BD or their healthy relatives, which showed impairments in verbal memory, attention, and executive functions notwithstanding a preserved level in measures of premorbid IQ (Robinson et al., 2006; Torres et al., 2007; Arts et al., 2008; Bora et al., 2009; Mann-Wrobel et al., 2011). Unfortunately, there were few data about neurocognitive functioning in specific domains at premorbid stage of BD. We found only two studies with small samples that explored this issue and reported impairments in executive function and visuospatial reasoning (Meyer et al., 2004; Ratheesh et al., 2013), suggesting that deficits in some specific domains might precede the onset of the disorder. Thus, these preliminary findings suggest that more research on the existence of domain-specific cognitive deficits prior to the onset of disorder is needed to conclude that there is a preserved cognitive status in the premorbid stage of BD. In particular, longitudinal studies assessing performance in specific cognitive domains in people with high risk of BD (offspring of parents with BD) and reassessing changes in neuropsychological tasks after the first episode among those later diagnosed as BD may be very useful. This approach would enable to simultaneously assess the presence of cognitive deficits in the premorbid stage as well as the change or not in cognition immediately after the onset of the disorder.

The general pattern of preserved general intelligence and impairments in specific domains in the premorbid stage which remain after the first episode that emerge in this review, also must be interpreted taking into account the possibility of the existence of subgroups of BD patients in terms of neurocognition. Different studies reported that there is a prevalence of 40–70% of adult patients without clinically significant cognitive impairments (Martino et al., 2008; Gualtieri and Morgan, 2008; Reichemberg et al.,2009; Iverson et al., 2011). A recent study found that a 30% of their sample of euthymic patients with BD were indistinguishable from healthy subjects in neurocognitive functioning while another 30% showed more severe deficits than those usually reported in literature (Martino et al., 2014). Another recent study identified three distinct neurocognitive subgroups of stable patients with BD: a group with performance comparable with healthy controls,

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a group with selective impairments, and a group with global deficits (Burdick et al., 2014). Then, it is possible to speculate that this heterogeneity in the neurocognitive functioning reported in patients with BD could also be observed in premorbid stage and in patients in their first episode of the disorder. For instance, although there is a trend to find a preserved level of general intelligence in the premorbid stage (Reichenberg et al., 2002; Cannon et al., 2002; Zammit et al., 2004), some studies reported higher IQ (Koenen et al., 2009) or increased performance on the arithmetic subtest (Tiihonen et al., 2005) than controls, and others low premorbid IQ in samples of early onset psychotic BD (Payá et al., 2013). These data resonate with the findings of another cohort study which found that either low or high grades in school increased the risk of mania (MacCabe et al., 2010). In addition, in the study by Olvet et al. (2010) BD patients do not differ with those of schizophrenia or healthy controls in terms of premorbid IQ and global neurocognitive score probably, at least in part, as a consequence of the high variance in the BD group. Similarly, variance in cognitive functioning might contribute to understanding differences in cognitive profile reported in the few studies in euthymic patients with first episode of BD (Nehra et al., 2006; Torres et al., 2010; López-Jaramillo et al., 2010). Therefore, some data from studies included in this review support the speculation that the heterogeneity in neurocognitive functioning in BD may extend to the premorbid stage and to the first episode of the disorder. This variability was also suggested from another recent review focused on the developmental trajectory of cognitive impairment in BD and schizophrenia (Bora, 2014). The heterogeneity in the neurocognitive profile of patients with BD might respond to quantitative or qualitative differences which could be also the focus of further studies (Martino et al., 2014).

In summary, considering BD as a group, to date there is evidence that general intelligence is not impaired in the premorbid stage, while very few studies assessed performance in specific cognitive domains both in the premorbid stage and after the first episode of the disorder. These studies bring preliminary support to the hypothesis that cognitive impairments in some specific domains are present at the first episode and might precede the onset of illness, although more research is needed to clarify this point. Finally, this general pattern does not exclude the possibility of identifying subgroups of patients with differences in neurocognition both in the premorbid stages as in the first episode of the disorder.

Conflict of interest

All authors declare that they have no conflicts of interest in relation with this work.

Contributors

All authors participated in the writing of the manuscript. Martino D designed the study and completed the review and led the writing of the manuscript. All authors contributed to and have approved the final manuscript.

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