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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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