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Attention impairment in bipolar disorder: a systematic review

Evelyn V. M. Camelo[1], Bruna Velasques[1], Pedro Ribeiro[1], Tania Netto[1], Elie Cheniaux[1,2]

1. Universidade Federal do Rio de Janeiro, Rio de Janeiro, RJ, Brazil

2. Universidade do Estado do Rio de Janeiro, Rio de Janeiro, RJ, Brazil

Abstract

Bipolar disorder (BD) has been associated with marked cognitive impairment, including euthymic periods. Attention is among the most compromised functions in BD. Changes related to learning, memory, and visuospatial abilities can be derived from these attention impairments. The objective of this article is to review the scientific literature on the performance of BD patients in attention tests. A systematic review was performed of controlled studies that assessed attention in patients diagnosed with BD aged between 18 and 65 years. The databases included Medline, LILACS, Cochrane Library, Institute for Scientific Information Web of Knowledge, and Scientific Electronic Library Online (SciELO), and the search encompassed the period from 2008 to 2013. Only studies that had a minimum sample of 10 patients were included. A total of 110 articles fulfilled the inclusion criteria. Compared with healthy control subjects, bipolar patients showed poorer attention performance. Compared with other mental disorders, BD was associated with poorer performance than unipolar depression but better performance than schizophrenia. When bipolar patients in different phases of the disease were compared with one another, the performance of euthymic patients was similar to or better than patients in a depressive state; moreover, manic patients performed worse than depressive patients. Attention is significantly impaired in BD. Attention impairment in BD is milder than in schizophrenia but greater than in unipolar depression. Attention impairment is possibly more severe in manic and depressed episodes than in euthymic periods.**Keywords:** attention, cognition, neuropsychological tests, bipolar disorder.

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Introduction

Cognitive deficits were first studied in brain injury and dementia and later in schizophrenia. However, since the 1970s, much effort has been devoted to understanding cognitive function in mood disorders, particularly bipolar disorder (BD; Caligiuri, & Ellwanger, 2000). The literature has provided evidence of stable and persistent cognitive impairments across the phases of BD, including euthymia, particularly in the following domains: sustained attention, learning, memory, visuospatial ability, and executive function (Caligiuri, & Ellwanger, 2000; Latalova, Jan, Tomas, Dana, & Hana, 2011). In BD, attentional changes are very relevant and can affect other cognitive functions, such as memory, learning, and executive function (Goodwin, Jaminson, & Ghaemi, 2007).

Numerous review articles have been published on cognitive impairments in BD, but these studies did not specifically address attention impairments (Sachs, Schaffer, & Winklbaur, 2007; Latalova et al., 2011; Kałwa, 2010; Quaishi & Frangou, 2002). To our knowledge, only one review article published 9 years ago (Clark, & Goodwin, 2004) focused specifically on attentional changes in bipolar patients. The present study provides an update on the knowledge of attention impairments in patients with BD by systematically reviewing controlled studies published in the past 5 years.

Methods

We performed a systematic review of the scientific literature on attention impairments in BD. References were identified in five databases (i.e., Medline, Institute for Scientific Information [ISI] Web of Knowledge, Cochrane Library, Scientific Electronic Library Online [SciELO], and LILACS) from 2008 to May, 27, 2013. The following search terms were used: “bipolar” and “attention” or “neuropsychological” or “cognition” or “cognitive.” The inclusion criteria were the following: samples with at least 10 patients diagnosed with BD, aged 18 and 65 years, and evaluations that used

Evelyn V. M. Camelo, Bruna Velasques, Pedro Ribeiro, and Elie Cheniaux, Universidade Federal do Rio de Janeiro, Instituto de Psiquiatria, Rio de Janeiro, RJ, Brazil. Tania Netto, Universidade Federal do Rio de Janeiro, Faculdade de Medicina, Departamento de Radiologia, Rio de Janeiro, RJ, Brazil. Elie Cheniaux, Universidade do Estado do Rio de Janeiro, Faculdade de Ciências Médicas, Rio de Janeiro, RJ, Brazil. Correspondence regarding this article should be directed to: Evelyn Camelo, Rua Ambrosina 100/202, Tijuca, 20540-120, Rio de Janeiro, RJ, Brazil. Phone: +55 (21) 9472-3522. E-mail: evypsi@gmail.com

neuropsychological tests that assessed attention. Only controlled trials (e.g., comparisons with healthy controls, with other mental disorders, or among BD patients in different affective states) were considered. Review articles, case reports, letters to the editor, and book chapters were excluded. No search of unpublished work was performed. Citations within a paper were also included as an additional source of references.

Results

The initial search retrieved 7,885 citations from Medline, 7396 from the ISI Web of Knowledge, 328 from Cochrane Library, 113 from SciELO, and 148 from LILACS, with some overlap among the databases. A total of 879 abstracts were classified as potentially relevant according to our criteria. After the appraisal of the full-text articles, 110 citations were selected.

Studies that compared BD patients with healthy control subjects

As shown in Table 1, 91 studies compared patients with a diagnosis of BD with healthy control subjects. In 80 of these studies, bipolar patients performed significantly worse in attention tests compared with healthy controls. In 11 studies, however, no significant difference was found between groups. In 53 of the 91 studies, the patients were not differentiated according to their mood state. In 36 of the 38 studies that incorporated such discrimination, both euthymic patients and patients in a manic or depressed state performed worse on attention tests than controls. One of these 38 studies found no significant difference between euthymic bipolar patients and healthy controls. Among the 80 studies in which the bipolar patients had poorer results compared with controls, sustained attention was evaluated in 40 studies, divided attention was evaluated in 42 studies, and selective attention was evaluated in 18 studies. Some of the studies evaluated more than one modality of attention.

Studies that compared BD with other mental disorders

As shown in Table 2, 15 studies compared BD patients with other mental disorders. In ten of these studies, comparisons were made with schizophrenia. The performance of bipolar patients on attention tests was significantly superior in seven of the ten studies. Among these seven studies, sustained attention was evaluated in four studies, and divided attention was evaluated in three studies. In two studies that evaluated divided and selective attention, no significant differences were found between the two groups. In only one study, patients with schizophrenia outperformed bipolar patients. In this study, sustained attention was assessed.

Five studies compared bipolar patients with unipolar depression patients. Sustained attention was evaluated in four of these studies. Selective attention was evaluated in two of these studies, and divided attention was evaluated in one of these studies. Unipolar depression patients had better attention performance in four of the five studies. No significant differences were found between the two groups in one study in measures of sustained and selective attention.

Studies that compared the different phases of BD

As seen in Table 3, four studies compared BD patients in different mood states. In two studies that evaluated sustained attention, euthymic bipolar patients were contrasted with patients in a depressed state. In one of these studies, euthymic patients had superior performance on attention tests, whereas no significant differences were found between groups in the other study. In the other two studies, depressive bipolar patients performed better than manic patients on tests that evaluated divided and selective attention.

Discussion

The present systematic review described controlled studies with bipolar patients who underwent neuropsychological evaluation using attention tests. Our aim was to provide an update on the body of knowledge about attention impairment in patients with BD based on studies published over the past five years.

According to our review, compared with health controls, patients with BD presented worse performance. Recently, other reviews that compared BD patients with healthy controls with regard to cognitive performance have been published (Thompson et al., 2005; Borges, Trentini, Bandeira, & DellÁglio, 2008; Burdick, Gunawardane, Goldberg, Halperin, Garno, & Malhotra, 2007; Rocca & Lafer, 2006). Our results on attention impairment in BD were very similar to those found in these reviews. These studies showed that cognitive impairment is part of the neuropsychological profile of BD patients. Specifically, these findings showed that these individuals have impairments in attention performance compared with healthy controls, regardless of whether the patients are euthymic, manic, or depressed. For example, Bora, Yücel, & Pantelis (2010) reviewed 12 studies that had samples with at least 10 subjects in each group, including patients with BD and healthy individuals, which were neurocognitively compared. All of these studies showed that patients with BD had inferior performance in tasks that measure executive function, memory, and attention.

According to our review, in seven of the ten studies that compared BD with schizophrenia, bipolar patients performed better in attention tests. Indeed, most of the review articles identified in the present study showed that patients cognitive deficits are more pronounced in patients with schizophrenia than in patients with BD in several cognitive functions, including psychomotor speed, verbal and visual memory, attention, and executive function (Goldberg et al., 1993; Evans, Heaton, Paulsen, McAdams, Heaton, & Jeste, 1999; Hawkins, Hoffman, Quinlan, Rakfeldt, Docherty, &

Table 1. Studies that compared bipolar patients with normal controls with regard to attention performance.

Study	Sample and design	Instruments	Type of attention	Results
Trivedi, Goel, Sharma, Singh, & Tandon, 2008	15 BD-e *vs.* 15 NC	CPT	Sustained attention	BD = NC
Morisano, Wing, Sacco, Arenovich, & Goerge, 2013	16 BD *vs.* 17 NC	CPT	Sustained attention	BD = NC
Gualtieri & Morgan, 2008	96BD *vs.* 907 NC	SCWT, CPT, SAT	Selective, sustained, divided attention	BD = NC
Frantom, Allen, & Cross, 2008	19 BD *vs.* 19 NC	SCWT, CPT, TMT	Selective, sustained, divided attention	BD = NC
Aydemir & Ender, 2009	38 BD *vs.* 19 NC	SCWT	Selective attention	BD = NC
Antila et al., 2009	39 BD *vs.* 55 NC	Digit Span, TMT	Divided attention	BD = NC
Torralva et al., 2011	15 BD *vs.* 15 NC	Digit Span, TMT	Divided attention	BD = NC
Tuulio-Henriksson et al., 2011	17 BD *vs.* 66 NC	Digit Span	Divided attention	BD = NC
Xu et al., 2012	223 BD *vs.* 202 NC	Digit Span	Divided attention	BD = NC
Wu et al., 2011	40 BD *vs.* 19 NC	Digit Symbol	Divided attention	BD = NC
Li et al., 2012	34 BD *vs.* 17 NC 80	Go/No-Go CPT	Divided attention Sustained attention	BD = NC
Burdick et al.,2011	BD-e *vs.*149 NC 126 BD	CPT		BD < NC
Schretlen et al.,2013	*vs.*340 NC		Sustained attention	BD < NC
Sanchez-Moreno et al., 2009	65 BD *vs.* 35 NC	Digit Span, TMT	Divided attention	BD < NC
Martino, Strejilevich, Torralva, & Manes, 2010	85 BD-e *vs.* 34 NC	Digit Span, TMT	Divided attention	BD < NC
Elshahawi,Essawi,Rabie,Mansour,Beshry,&Mansour,2011	100 BD-e *vs.* 50 NC	TMT	Divided attention	BD < NC
Normala, Abdul, Azlin, Nik, Hazli, & Shah, 2010	40 BD *vs.* 40 NC	Digit Span, TMT	Divided attention	BD < NC
Burdick et al.,2011	103 BD-e *vs.* 35 NC	Digit Span, TMT	Divided attention	BD < NC
Torrent et al., 2011	79 BD-e *vs.* 35 NC	Digit Span, TMT	Divided attention	BD < NC
Martino et al., 2011a	87 BD-e *vs.* 39 NC	Digit Span, TMT	Divided attention	BD < NC
Martino et al., 2011b	81 BD-e *vs.* 34 NC	Digit Span, TMT	Divided attention	BD < NC
Bonnín et al., 2012	103 BD-e *vs.* 30 NC	Digit Span, TMT	Divided attention	BD < NC
Torrent et al., 2012	68 BD-e *vs.* 45 NC	Digit Span, TMT	Divided attention	BD < NC
Pattanayak, Sagar, & Mehta, 2012	30 BD-e *vs.* 20 NC	Digit Span, TMT	Divided attention	BD < NC
Martino et al., 2008	50 BD *vs.* 30 NC	Digit Span, TMT, CPT	Divided, sustained attention	BD < NC
Soeiro-de-Souza, Machado-Vieira, Soares Bio, Do Prado, & Moreno, 2012	66 BD *vs.* 78 NC	Digit Span, TMT, SCWT	Divided, selective attention	BD < NC
Soeiro-de-Souza et al., 2012	72 BD *vs.* 76 NC	Digit Span, TMT, SCWT	Divided, selective attention	BD < NC
Hill et al., 2009	22 BD *vs.* 41 NC	Digit Span, CPT	Divided, sustained attention	BD < NC
Jabben, Krabbendam, & van Os, 2009	76 BD *vs.* 61 NC	Digit Span, CPT	Divided, sustained attention	BD < NC
Thompson, Gray, Crawford, Hughes, Young, & Ferrier, 2009	63 BD-e *vs.* 63 NC	Digit Span, CPT, TMT SCWT, COWA, TL	Divided, sustained, selective attention	BD < NC
Mur et al., 2008b	15 BD *vs.* 15 NC	Digit Span, SCWT	Divided, selective attention	BD < NC
Simonsen et al., 2008	73 BD *vs.* 124 NC	Digit Span	Divided attention	BD < NC
Barrett et al., 2009	32 BD-m *vs.* 67 NC	Digit Span	Divided attention	BD < NC
Gogos, Joshua, & Rossell, 2010	40 BD *vs.* 43 NC	Digit Span	Divided attention	BD < NC
Vaskinn, Sundet, Simonsen, Hellvin, Melle, & Andreassen, 2011	106 BD *vs.* 340 NC	Digit Span	Divided attention	BD < NC
Yates, Dittmann, Kapczinski, & Trentini, 2011	65 BD *vs.* 34 NC	Digit Span	Divided attention	BD < NC
Dickerson et al., 2011	60 BD *vs.* 312 NC	Digit Span	Divided attention	BD < NC
Gerber et al., 2012	30 BD-e *vs.* 20 NC	Digit Span	Divided attention	BD < NC
Chou et al., 2012	23 BD-e *vs.* 33 NC	Digit Span	Divided attention	BD < NC
Soeiro-de-Souza, Bio, Dias, Vieta, Machado-Vieira, & Moreno, 2013	109 BD *vs.* 96 NC	Digit Span	Divided attention	BD < NC
Burdick et al., 2009	24 BD *vs.* 24 NC	SCWT	Selective attention	BD < NC
Pompei et al., 2011	39 BD-e *vs.* 48 NC	SCWT	Selective attention	BD < NC
Lewandowski et al., 2011	31 BD *vs.* 20 NC	SCWT	Selective attention	BD < NC
Juselius, Kieseppa, Kaprio, Lonnqvist, & Tuulio-Henriksson, 2009	26 BD-e *vs.* 114 NC	TMT	Divided attention	BD < NC
Solé et al., 2012	43 BD *vs.* 42 NC	TMT	Divided attention	BD < NC
Chang et al., 2012	94 BD *vs.* 29 NC	TMT	Divided attention	BD < NC
Benson et al., 2008	30 BD *vs.* 66 NC	CPT	Sustained attention	BD < NC
Mur et al., 2008a	33 BD *vs.* 33 NC	CPT	Sustained attention	BD < NC
Tabarés-Seisdedos et al., 2008	43 BD *vs.* 25 NC	CPT	Sustained attention	BD < NC

Study	Sample and design	Instruments	Type of attention	Results
Malloy-Diniz, Neves, Abrantes, Fuentes, & Correa, 2009	39 BD *vs.* 53 NC	CPT	Sustained attention	BD < NC
Strakowski et al., 2009	70 BD-m *vs.* 34 NC	CPT	Sustained attention	BD < NC
Lahera et al., 2009	24 BD-e *vs.* 38 NC	CPT	Sustained attention	BD < NC
Swann, Lijffijt, Lane, Steinberg, & Moeller, 2009	112 BD *vs.* 71 NC	CPT	Sustained attention	BD < NC
Sanchez-Morla et al., 2009	73 BD-e *vs.* 67 NC	CPT	Sustained attention	BD < NC
Brooks, Bearden, Hoblyn, Woodard, & Ketter, 2010	16 BD-e *vs.* 11 NC	CPT	Sustained attention	BD < NC
Van der Wer-Eldering, Burger, Holthausen, Aleman, & Nolen, 2010	110 BD *vs.* 75 NC	CPT	Sustained attention	BD < NC
Ancín et al., 2011	143 BD-e *vs.* 101 NC	CPT	Sustained attention	BD < NC
Van der Wer-Eldering, Burger, Jabben, Holthausen, Aleman, & Nolen, 2011	108 BD *vs.* 75 NC	CPT	Sustained attention	BD < NC
Arts et al., 2011	76 BD *vs.* 61 NC	CPT	Sustained attention	BD < NC
Pan, Hsieh, & Liu, 2011	32 BD-e *vs.* 39 NC	CPT	Sustained attention	BD < NC
Howells, Ives-Keliperi, Horn, & Stein, 2012	12 BD-e *vs.* 9 NC	CPT	Sustained attention	BD < NC
Sepede et al., 2012	24 BD-e *vs.* 24 NC	CPT	Sustained attention	BD < NC
Donohoe et al., 2012	110 BD *vs.* 163 NC	CPT	Sustained attention	BD < NC
Fleck et al., 2012	50 BD *vs.* 34 NC	CPT	Sustained attention	BD < NC
Lee, Altshuler, Glahn, Miklowitz, Ochsner, & Green, 2013	68 BD *vs.* 36 NC	CPT	Sustained attention	BD < NC
Cummings et al., 2013	125 BD *vs.* 171 NC	CPT	Sustained attention	BD < NC
Strakowski et al., 2010	108 BD-m *vs.* 48 NC	DSCPT	Sustained attention	BD < NC
Hellvin et al., 2012	55 BD-m *vs.* 110 NC	DSCPT	Sustained attention	BD < NC
Holmes et al., 2008	65 BD-d *vs.* 52 NC	RVIP	Sustained attention	BD < NC
Roiser et al., 2009	49BD-d *vs.* 55 NC	RVIP	Sustained attention	BD < NC
Maalouf et al., 2010	52 BD *vs.* 28 NC	RVIP	Sustained attention	BD < NC
Yoram et al., 2013	47 BD *vs.* 31 NC	RVIP	Sustained attention	BD < NC
Vierck et al., 2013	96 BD *vs.* 24 NC	RVIP	Sustained attention	BD < NC
Chaves et al., 2011	29 BD *vs.* 30 NC	IP-CPT, Digit Span	Sustained, divided attention	BD < NC
Mora, Portella, Forcada, Vieta, & Mur, 2012	28 BD-e *vs.* 26 NC	CPT, Digit Span, SCWT	Sustained, divided, selective attention	BD < NC
Iverson et al., 2011	43 BD *vs.* 659 NC	CPT, SCWT	Sustained, selective attention	BD < NC
Levy, 2013	30 BD-e *vs.* 22 NC	CPT, SCWT	Sustained, selective attention	BD < NC
Iverson et al., 2009	47 BD *vs.* 47 NC	CPT, SCWT, SAT	Sustained, selective, divided, attention	BD < NC
Martinez-Aran et al., 2008	65 BD-e vs. 35 NC	TMT, SCWT	Divided, selective attention	BD < NC
López-Jaramillo et al., 2010b	40 BD-e vs. 20 NC	TMT, SCWT	Divided, selective attention	BD < NC
Marshall et al., 2012	256 BD vs. 97 NC	TMT, SCWT	Divided, selective attention	BD < NC
Doğanavşargil, Bokmen, Akbas, Cinemre, Metin, & Karaman, 2013	60 BD-e vs. 20 NC	TMT, SCWT	Divided, selective attention	BD < NC
López-Jaramillo et al., 2010a	98 BD-m vs. 66 NC	TMT, SCWT, CT	Divided, selective attention	BD < NC
Torres et al., 2010	45 BD vs. 25 NC	TMT, SCWT, RVIP, CVLT-II	Divided, selective, sustained attention	BD < NC
Cuesta et al., 2011	65 BD *vs.* 76 NC 60	TMT, Digit Span Digit	Divided attention	BD < NC
Watson et al.,2012	BD-d *vs.*55 NC	Symbol	Divided attention	BD < NC
Pradhan, Chakrabarti, Nehra, & Mankotia, 2008	48 BD-e *vs.* 23 NC	PGIMS	Selective attention	BD < NC
Wobrock et al., 2009	18 BD *vs.* 23 NC	TMT	Divided attention	BD > NC
Mahlberg, Adli, Bschor, & Kienast, 2008	28 BD-m *vs.* 30 BD-d	TMT	Divided attention	BD > NC
Liu, Chen, Hsieh, Su, Yeh, & Chen, 2010	27 BD *vs.* 21 NC	TAP	Divided attention	BD < NC
Shan et al., 2011	69 BD *vs.* 22 NC	Digit Symbol	Sustained attention	BD < NC

>, better performance; <, worse performance; =, similar performance. BD, bipolar disorder; NC, normal control; SZ, schizophrenia; UP, unipolar depression; BD-e, bipolar disorder, euthymic; BD-d, bipolar disorder, depressive; BD-m, bipolar disorder, manic; TMT, Trail Making Test; CPT, Continuous Performance Test ; CPTII, Continuous Performance Test II, version 5; PCTP, Penn Continuous Performance Test; CPT-IP, Continuous Performance Test, identical pairs version; DS-CPT, Degraded Stimulus Continuous Performance Test; CPT-AX, Continuous Performance Test-AX (a character or number preceded by another character or number as a target); RVIP, Rapid Visual Information Processing; SCWT, Stroop Color Word Test; CT, Cancellation Test; SAT, Shifting Attention Test; CB, conditioned blocking; CVLT-II, California Verbal Learning Test; TAP, Attentional Performance Test; TL, Tower of London; COWA, Controlled Oral Word Association Test; PGIMS, PGI memory scale; PASAT, Paced Auditory Serial Addition.

Table 2. Studies that compared attention performance in bipolar disorder and other mental disorders.

Study	Sample and design	Instrument	Type of attention	Results
Gogos et al., 2009	12 BD-e *vs.* 28 SZ	Digit Span	Divided attention	BD > SZ
Barret et al., 2009	32 BD-m *vs.* 44 SZ	Digit Span, CB	Divided attention	BD > SZ
Cuesta et al., 2011	65 BD *vs.* 86 SZ	Digit Span, TMT	Divided attention	BD > SZ
Tabarés-Seisdedos et al., 2008	43 BD *vs.* 47 SZ	Asarnow CPT	Sustained attention	BD > SZ
Lee et al., 2013	68 BD *vs.* 38 SZ	CPT	Sustained attention Sustained	BD > SZ
Schretlen et al.,2013	126 BD vs.110 SZ	CPT	attention	BD > SZ
Cummings et al., 2013	125 BD *vs.* 573 SZ	CPT	Sustained attention	BD > SZ
Pradhan et al., 2008	48 BD-e *vs.* 32 SZ	PGIMS	Selective attention	BD = SZ
Wobrock et al., 2009	18 BD *vs.* 24 SZ	TMT	Divided attention	BD = SZ
Donohoe et al., 2012	110 BD *vs.* 487 SZ	CPT	Sustained attention	BD < SZ
Benson et al., 2008	30 BD *vs.* 34 UP	CPT	Sustained attention	BD < UP
Iverson et al., 2011	43 BD *vs.* 143 UP	CPT, SCWT	Sustained, selective attention	BD < UP
Xu et al., 2012	223 BD *vs.* 293 UP	Digit Span	Divided attention	BD < UP
Maalouf et al., 2010	18 BD-e *vs.* 14 BD-d *vs.* 20 UP	RVIP	Sustained attention	BD-e < UP BD-d < UP
Gualtieri & Morgan, 2008	96 BD *vs.* 285 UP	CPT, SCWT	Sustained, selective attention	BD = UP

See Table 1 for abbreviations

Table 3. Studies that compared attention performance in the different phases of bipolar disorder.

Study	Sample and design	Instruments	Types of attention	Results
Maalouf et al., 2010	18 BD-e *vs.* 14 BD-d	RVIP	Sustained attention	BD-e = BD-d
Van der Wer-Eldering et al., 2011	45 BD-e *vs.* 63 BD-d	CPT	Sustained attention	BD-e > BD-d
Mahlberg et al., 2008	28 BD-m *vs.* 30 BD-d	TMT	Divided attention	BD-d > BD-m
Soeiro-de-Souza et al., 2012	41 BD-m *vs.* 25 BD-d	Digit Span, TMT, SCWT	Divided, selective attention	BD-d > BD-m

See Table 1 for abbreviations

Sledge, 1997; Rocca & Lafer, 2006; Quaishi & Frangou, 2002). For example, Daban et al. (2006) selected 38 studies that compared BD and schizophrenia patients during the execution of neuropsychological tasks. Patients with BD performed better on tasks that measured Intelligence Quotient (IQ), attention, memory, and executive function. The authors proposed that the poor performance in schizophrenia patients occurred because of the presence of psychotic symptoms, the duration of the illness, and hospitalization. Simonsen et al. (2008) found that BD patients with psychotic symptoms have similar performance as schizophrenia patients in some neurocognitive tasks, such as verbal memory and processing speed. Some authors (Andreasen, & Powers, 1974; Strauss, Bohannon, Stephens, & Pauker, 1984; Goldberg et al., 1993; Evans et al., 1999) believe that defining the mood state in samples of BD patients is important because manic patients perform worse than depressive or euthymic patients in working memory, selective attention, and divided attention tasks, and manic patients perform similarly to schizophrenia patients.

We found only five studies that compared BD patients with unipolar depression patients by applying attention tests. In four of these studies, BD patients had worse performance (Benson et al., 2008; Xu et al., 2012; Maalouf et al., 2010). According to other review articles (Rocca & Lafer., 2006; Murphy & Sahakian, 1999), patients with BD present worse performance than unipolar depression patients not only in attention tests but also in several other cognitive tasks, such as executive function and working memory.

Our search found only four studies that compared BD patients in different mood states (i.e., euthymia, mania, and depression). In two studies, manic patients presented worse performance than depressed patients. However, the distinction between depressed and euthymic patients was less evident. Two articles (Martínez-Arán et al., 2009; Rocca & Lafer, 2006) showed that euthymic patients had difficulty in cognitive tasks, but this impairment was less severe compared with depressive and manic patients. Some review articles (Van Gorp, Altshuler, Theberge, Wilkins, & Dixon, 1998; Cavanagh, Van Beck, Muir, & Blackwood, 2002; Clark, Iversen, & Goodwin, 2002; Deckersback, McMurrich, Ogutha, Savage, Sachs, & Rauch, 2004) reported consistent deficits in sustained attention, verbal memory, and executive function in mania. Moreover, patients with BD in the depressive or euthymic phase performed better than manic patients in attention tasks (Zubieta, Huguelet, O'Neil, & Giordani, 2001; Clark et al., 2002; Thompson et al., 2005; Xu et al., 2012), verbal learning (Clark et al., 2002; Deckersbach et al., 2004), and visual memory (MacQueen & Young, 2003; Deckersbach et al., 2004).

One hypothesis that may explain the worse performance in manic patients in sustained attention tests is related to the typical impulsivity exhibited by these patients. They answer quickly and incorrectly

before the stimulus appears, thus impairing their performance. Impairments in sustained attention were observed in the Continuous Performance Test (CPT), which represents a central neuropsychological deficit associated with mania (Murphy et al., 1999).

Attention is a complex system related to the activation of other cognitive functions; thus, attention impairments in BD patients can be primarily related to other cognitive dysfunctions (Van Gorp et al., 1998; Martínez-Arán et al., 2009). In BD, alterations in attention are highly relevant and can affect other cognitive functions, such as learning, executive function, and memory (Goodwin et al., 2007).

Cognitive deficits become worse over the course of BD (Vieta, 2012; Levy et al., 2009) and are associated with a greater number of disease episodes (Vieta et al., 2012). Selva et al. (2007) failed to find differences between psychotic and non-psychotic subjects on a series of memory, executive function, and attention tests. Harkavy-Friedman et al. (2006) found that suicide attempters with BD had worse performance than non-suicidal bipolar patients in psychomotor performance, working memory, attention, and impulse control.

Patients with BD generally exhibit typical cognitive development premorbidly but exhibit deficits by the first episode that are amplified as the symptoms worsen. Some data suggest that cognitive deficits may precede the onset of mania; therefore, identifying cognitive predictors of bipolar disorder would be beneficial to facilitate early intervention (Lewandowski, Cohen, Keshavan, & Ongür, 2011; Olvet, Burdick, & Cornblatt, 2013).

First-episode mania patients were found to have less neurocognitive deficits in psychomotor speed, attention, learning and memory, executive function, and IQ compared with multiple-episode patients (Hellvin et al., 2012; Van Gorp et al., 1998).

Psychiatric medications commonly used in BD can affect cognition. According to some review articles (Honig, Arts, Ponds, & Riedel, 1999; Pachet, & Wisniewski, 2003), lithium may exert mild negative effects in tasks of verbal memory and psychomotor speed, whereas visuo-spatial performance, attention, and executive performance are spared. Lithium has also been shown to exert a neuroprotective effect and be related to better cognitive performance in patients with BD (Bauer, Alda, Priller, & Young, 2003). Atypical antipsychotics have shown more negative effects on cognition compared with lithium and anticonvulsants (Arts, Jabben, Krabbendam, & van Os, 2011; Macqueen, & Young, 2003; Torrent et al., 2011; Yurgelun-Todd et al., 2002).

Some studies have reported that cognitive impairment in patients with BD represents a trait marker of the disease (Clark et al., 2004). These studies have proposed a neurodegenerative hypothesis to explain the cognitive deficits associated with BD (McKinnon, Cusi, & Macqueen, 2012). Cognitive damage would be an endophenotype of the disorder and a marker associated with this mental disorder. The term "endophenotype" was used by Gottesman (2003) to describe a trait that may be intermediate on the chain of causality from genes to diseases. Some family relatives of affected patients also carry the endophenotype, although not the disorder phenotype (i.e., affective symptoms) in the case of BD (Adida et al., 2012). In fact, some studies also described attention deficits in unaffected relatives of individuals with mood disorders (Bora, Yucel, & Pantelis, 2009; Brotman, Rooney, Skup, Pine, & Leibenluft, 2009; Grunebaum, Cohler, Kauffman, & Gallant, 1978; Klimes-Dougan, Ronsaville, Wiggs, & Martinez, 2006; Zalla et al., 2004).

Gottesman, & Gould (2003) discussed endophenotypes and suggested five criteria that should be characteristic of a trait to qualify it as an endophenotype. These five criteria are used to assess the viability of using measures of neuropsychological dysfunction as endophenotypes for genetic studies of BD (Savitz, Solnes, & Ramesar, 2005). The importance of early interventions in BD have been extensively studied, and recent efforts have been made to identify individuals who are at increased risk; e.g., relatives of bipolar patients (Bora et al., 2009; Olvet et al., 2013). For this reason, some researchers have recently begun to focus on the genetic contributions to discrete (as opposed to global) cognitive processes, such as executive function, working memory, and attention. For example, a version of executive function evaluated by selective and sustained attention tests, e.g., WCST and CPT (Conners, 2000) was reported to have a degree of heritability (Savitz et al., 2005).

To demonstrate that a trait is an endophenotype, the trait must be shown to be mood state-independent and heritable (Gottesman, & Gould, 2003). Thus, studies that examine neurocognitive aspects and neuroanatomic changes, together with genetics studies, are important to improve our understanding of the neural basis of BD (Kurnianingsih, Kuswanto, McIntyre, Qiu, Ho, & Sim, 2011).

Considering the neuroanatomic changes that occur in BD, a correlation has been found between a longer disease duration and more pronounced atrophy in the frontal cortex, an area that is closely related to attention (Stoll, Renshaw, Yurgelun-Todd, & Cohen, 2000; Kemptom, Geddes, Ettinger, Williams, & Grasby, 2008). Studies of bipolar patients tested attentional impairment using the CPT and structural and functional magnetic resonance imaging and reported changes in the dorsolateral prefrontal cortex (Rocca & Lafer, 2006), prolonged amygdala overactivation, and prefrontal cortex atrophy (Sax, Strakowski, Zimmerman, DelBello, Keck, & Hawkins, 1999). In addition to these findings, other studies have reported that certain neuroanatomic structures are associated with attention dysfunction during mania (Sax et al., 1999). One such structure is the right prefrontal cortex, which appears to be involved in sustained attention (Manly, & Robertson, 1997). Furthermore, functional neuroimaging studies of bipolar patients have detected activation in the right prefrontal cortex during the

assessment of sustained attention (Coull, Frith, Frackowiak, & Grasby, 1996; Paus, Zatorre, & Hofle, 1997). Other modalities of attention, such as selective and divided attention, have also been associated with functional or structural alterations. In patients with BD, a reduction of neural responsiveness was observed in regions involved in selective attention within the posterior and inferior parietal lobes (Pompei et al., 2011). Additionally, impairment in divided attention in patients with bipolar depression has been attributed to a reduction of attentional resources by the central executive (i.e., the working memory component) and impaired activation in the frontal lobe (Paus, Zatorre, & Hofle, 1997). According to the results of the present review, all types of attention are significantly impaired in BD (Ancín et al., 2011; Andersson, Barder, Hellvin, Løvdahl, & Malt, 2008; Barrett, Mulholland, Cooper, & Rushe, 2009; Bonnín et al., 2012; Burdick et al., 2009; Iverson, Brooks, & Young, 2009). Specifically, sustained attention and divided attention are more severe in mania and in depression, respectively (Murphy et al., 1999).

Attentional impairment in BD is less severe than in schizophrenia but greater than in unipolar depression and possibly more severe in the mania and depression phases of BD than in the euthymia phase. These findings have prompted us to propose the development of cognitive rehabilitation techniques for individuals with BD that are similar to those used for persons with frontal lobe dysfunction (Levine, Turner, & Stuss, 2008) or brain injury (Ponsford, 2008). Attention is directly related to other cognitive functions, such as learning, memory, and executive function. Alterations in these and other cognitive functions could at least partially derive from attention deficits. Further studies are needed to investigate the attention alterations in BD, especially longitudinal studies that would allow an enhanced understanding of the progressive character of attention deficits in BD.

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