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Neurocognitive functioning in euthymic patients with bipolar disorder and unaffected relatives: A review of the literature

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Abstract

Background—Neurocognitive deficits are present in bipolar disorder (BD) patients and their unaffected (nonbipolar) relatives, but it is not clear which domains are most often impaired and the extent of the impairment resulting from shared genetic factors. In this literature review, we address these issues and identify specific neurocognitive tasks most sensitive to cognitive deficits in patients and unaffected relatives.

Method—We conducted a systematic review in Web of Science, PubMed/Medline and PsycINFO databases.

Results—Fifty-one articles assessing cognitive functioning in BD patients (23 studies) and unaffected relatives (28 studies) were examined. Patients and, less so, relatives show impairments in attention, processing speed, verbal learning/memory, and verbal fluency.

Conclusion—Studies were more likely to find impairment in patients than relatives, suggesting that some neurocognitive deficits may be a result of the illness itself and/or its treatment. However, small sample sizes, differences among relatives studied (e.g., relatedness, diagnostic status, age), and differences in assessment instruments may contribute to inconsistencies in reported neurocognitive performance among relatives. Additional studies addressing these issues are needed.

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Declaration of interests

The authors declare no conflict of interests.

Keywords

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Patients with bipolar disorder (BD) show cognitive deficits across a range of domains. This is true during acute mood episodes (Gruber et al., 2007; Malhi et al., 2007; Martinez-Aran et al., 2004; Quraishi and Frangou, 2002), but also during euthymic periods (for reviews, see Robinson et al., 2006; Torres et al., 2007), suggesting that deficits represent trait-like features of BD (Gottesman and Gould, 2003). Neurocognitive domains consistently reported to be impaired in BD include executive functioning, verbal memory, verbal fluency, and sustained attention (Balanza-Martinez et al., 2008; Mann-Wrobel et al., 2011; Torres et al., 2007). However, little is known about which cognitive deficits precede a bipolar disorder diagnosis and which develop as a result of illness onset and treatment. One widely used approach to distinguish primary traits (or endophenotypes) from those that are a consequence of illness or its treatment is to study individuals at familial risk (Gottesman and Gould, 2003).

Family studies show that about 7–22% of first-degree relatives of BD patients will develop a major mood disorder (Merikangas et al., 2002). Some recent research has shown that unaffected, at-risk relatives have a higher incidence of cognitive impairment than the general population (see Olvet et al., 2013), for a recent review). Deficits present in unaffected (nonbipolar) at-risk relatives cannot be due to illness or treatment and may thus reveal neurocognitive traits that reflect an underlying diathesis.

The International Society for Bipolar Disorders (ISBD) has proposed a consensus-based battery for the assessment of neurcognition in BD (Yatham et al., 2010). Two recent studies have tested the suitability of the proposed ISBD tasks with promising results (Bourne et al., 2013; Van Rheenen and Rossell, 2014). Still, no one has assessed the utility of the proposed tasks in detecting cognitive impairments in *relatives* of BD patients. Although the ISBD's final proposed cognitive battery for BD coincides with the current review's findings in regards to tasks appropriate for use with bipolar patients, the potential utility of the tasks with a BD relative population is not addressed.

The current study employs a systematic literature search to ascertain which neurocognitive domains are found to be consistently affected among both patients with bipolar disorder and unaffected individuals at familial risk of BD. Due to differences in research methodologies that have resulted in large inconsistencies in effect sizes and even in the nature of impairments reported, we also aimed to generate a list of viable candidate cognitive measures for use in a consensus-based battery.

1. Methods

1.1. Search strategy

Published reports investigating neuropsychological function in *patients with bipolar disorder* were identified through a systematic literature search in the Web of Science, PubMed/Medline and PsycINFO electronic databases covering the period between January 2000 and

October 2014, using the keywords ‘bipolar disorder’; ‘euthymi*’ and ‘test’; ‘assessment’ or ‘battery’ with ‘cognit*’ or ‘neuropsych*’. This search strategy yielded 395 articles.

To identify studies investigating neuropsychological function in *unaffected (nonbipolar) relatives* of patients with BD the same strategy was employed plus the terms ‘famil* risk’, ‘first degree relative’, ‘at risk’, ‘genetic risk’, ‘unaffected sibling’, ‘famil* vulnerab*’, or ‘unaffected relative’ were searched. In light of the widely cited meta-analyses published by Arts et al. (2008) and Bora et al. (2009), articles investigating neuropsychological function in unaffected *relatives* published before 2008 were excluded from this work to avoid redundancy. All three databases were searched on the same day and searches were limited to English language articles with abstracts. These search strategies generated approximately 123 articles, most of which were found on Web of Science (see Fig. 1).

1.2. Study selection

Publication titles and abstracts were reviewed for all inclusion/exclusion criteria. Inclusion and exclusion criteria differed for studies involving *patients with bipolar disorder* and for studies involving *relatives of patients with bipolar disorder*.

The first search resulted in 395 articles involving *participants with bipolar disorder*. Inclusion criteria for studies investigating neurocognitive functioning in patients with BD: (1) patients 18–65 diagnosed with bipolar disorder (e.g., BPI, BPII, BPNOS) currently in a remitted state; (2) at least one measure of neurocognitive function; (3) neurocognitive data pertaining to euthymic patients with BD as a distinct group; and (4) inclusion of a healthy control group for comparison. Articles were excluded if (1) they did not present original findings (e.g., reviews, meta-analyses, or opinion papers) (56 studies); or (2) did not provide complete information on sample size, mood state, or selection criteria (13 studies). After all inclusion and exclusion criteria were assessed, 168 articles were identified. Articles were sorted based on total number of euthymic patients with BD tested. To make results easier for the readers to interpret, we eliminated studies with smaller sample sizes, which are prone to overestimation of cognitive deficits due to publication bias. To avoid an arbitrary selection, we estimated the median sample size of qualifying studies (34), and selected studies whose sample size was at least one standard deviation above this value. Sample sizes of the selected studies ranged from 68 to 256. This resulted in 23 articles that assessed neurocognitive function in euthymic patients with BD that are used for this literature review (Table 1).

The second search resulted in 123 articles involving *relatives of patients with BD*. Inclusion criteria for studies investigating neurocognitive functioning in *relatives*: (1) provided neuropsychological data pertaining to *relatives* as a distinct group; (2) included a healthy comparison group with no prior history of bipolar disorder or current neuropsychiatric illness and no relatives with BD; (3) included *relatives* with no personal history of BD. Twenty-eight articles met our inclusion/exclusion criteria and are included in this review (Table 2); sample sizes ranged from 7 to 580. Notably, due to the limited availability of studies investigating neurocognitive function in *relatives*, age was not considered among the exclusion criteria. Relatives in the studies included in this review were often described as ‘first-degree relatives’, ‘parents’, ‘siblings’, or ‘offspring’; some studies did not specify the nature of the relationship between the relative and the affected proband. Although a few of

the studies investigating neurocognitive functioning in individuals at familial risk also tested patients with BD, results from these patients were not included in this review due to comparatively small sample sizes reported (median of N = 38).

In sum, fifty-one articles evaluating neurocognitive function in patients with BD (23 studies) and in relatives of patients with bipolar disorder (BD-RLs) (28 studies) are included in the current literature review.

1.3. Neuropsychological domains measured by selected cognitive instruments

Performance on cognitive tests often encompasses a diverse set of cognitive functions. At any given time the use of more than one cognitive function (e.g., cognitive flexibility and visual attention) may be required to fulfill the goals set forth by the given task (e.g., TMT-A). A similar issue arises when a given instrument (e.g., WMS Digit Span Test) is used to test different domains by different researchers in separate studies (e.g., attention or verbal working memory). This overlap creates challenges for researchers attempting to classify cognitive tests into individual domains. As a result, researchers may not always follow the same classification of cognitive tests. In an attempt to establish consistency, we followed Strauss et al. (2006)'s classification system. We also explicitly report on tasks employed in each of the studies reviewed. References and descriptions of the various cognitive instruments detailed can be found elsewhere (Strauss et al., 2006).

2. Results

The following results are described in terms of studies and specific measures or tests assessing patients with BD or relatives of patients with BD. For any given study, multiple measures assessing a variety of neuropsychological domains may have been utilized. When relevant, fractions are used to describe the number of tasks or studies for which BD patients and relatives showed deficits (numerator) and the total number of tasks or studies that tested a given function (denominator). Results described below do not encompass the entirety of instruments utilized by studies included in this review. For a more comprehensive list of results with all instruments used by the studies we reviewed see Table 2 (for relatives of BD patients), Table 3 (for BD patients and relatives), and Table 4 (for BD patients).

2.1. Intelligence

Forty studies used several instruments to estimate intelligence (BD, 22 studies; BD-RLs, 18 studies). Overall intelligence seemed to be impaired among *patients with BD* in over half of measures, whereas it may be preserved in *relatives*, since their performance was similar to controls on most measures of intelligence.

The Wechsler Adult Intelligence Scale (WAIS) vocabulary subtest was used most consistently to measure intelligence among patients and relatives. Performance by *bipolar participants* on this task was equally mixed between scores that were similar to, or lower than controls (Bonnin et al., 2012; Marshall et al., 2012; Martino et al., 2011a,b, 2014; Ryan et al., 2013; Torrent et al., 2006) (Ancin et al., 2013, 2010; Elshahawi et al., 2011; Martinez-Aran et al., 2009, 2007; Sanchez-Morla et al., 2009; Santos et al., 2014; Torrent et al., 2011). Among *relatives* intelligence was shown to be mostly preserved when tested using this task

(Antila et al., 2009; Christodoulou et al., 2012; Daban et al., 2012; Doyle et al., 2009; Fears et al., 2014; Quraishi et al., 2009; Schulze et al., 2011; Thermenos et al., 2010). Notably, three of the studies that found preserved intelligence among relatives had large sample sizes (N = 580; N = 557; N = 118) (Daban et al., 2012; Doyle et al., 2009; Fears et al., 2014).

Among *first-degree relatives*, preserved intelligence was also observed in five studies using the WAIS *current full-scale* intelligence quotient (FSIQ) (Brotman et al., 2009; Christodoulou et al., 2012; Doyle et al., 2009; Kumar et al., 2010; Quraishi et al., 2009), with one exception, which showed impaired functioning in this task (Maziade et al., 2009). Various other tasks, mostly derived from individual WAIS subtests (e.g., Block Design, Object Assembly, Similarities, and Comprehension) were utilized to test intelligence in other studies. However, use of these tasks was often limited to one or two studies, precluding any conclusive remarks. While there is some evidence for impaired general intelligence in *patients*, there is no consistent evidence of impairment in this domain among *relatives* suggesting that intelligence measures may be more sensitive to capturing the effects of the illness and/or its treatment.

2.2. Executive function

The broad neuropsychological domain of executive function was assessed in 35 studies among *patients with BD* (20 studies) and *relatives* (15 studies) using several measures. Executive function was impaired among *patients with BD*, but preserved among *relatives* in the majority of reports.

2.2.1. Cognitive flexibility and response inhibition—This function was assessed in 32 studies among *patients* (19 studies) and *relatives* (13 studies) using several tests. Response inhibition evaluated with the Stroop Colour Word Test (SCWT) and variants was impaired in *patients with BD* in the majority of studies (Ancin et al., 2013; Brissos et al., 2011; Dias et al., 2008; Marshall et al., 2012; Martinez-Aran et al., 2009, 2007; Palsson et al., 2013; Ryan et al., 2013; Sanchez-Morla et al., 2009; Santos et al., 2014; Simonsen et al., 2011; Torrent et al., 2006) with a few exceptions (Bonnin et al., 2012; Torrent et al., 2011). When cognitive flexibility was assessed with the Trail Making Test-Part B (TMT-B), a similar pattern emerged: the majority of studies found significant impairment among *patients* (Ancin et al., 2013; Bonnin et al., 2012; Brissos et al., 2011; Dias et al., 2008; Dittmann et al., 2008; Elshahawi et al., 2011; Marshall et al., 2012; Martinez-Aran et al., 2009, 2007; Martino et al., 2011b, 2014; Palsson et al., 2013; Ryan et al., 2013; Sanchez-Morla et al., 2009; Santos et al., 2014), with few exceptions (Torrent et al., 2006, 2011).

Among *relatives*, cognitive flexibility, as measured by the TMT-B, was also impaired in three studies (Antila et al., 2009; Civil Arslan et al., 2014; Erol et al., 2014; Glahn et al., 2010). Although, several studies found no deficits in *unaffected first-degree relatives* (Antila et al., 2011; Civil Arslan et al., 2014; Kulkarni et al., 2010), or high risk offspring of BD (Deveci et al., 2013). When tested with the SCWT, *relatives* were impaired nearly as often (Doyle et al., 2009; Erol et al., 2014; Fears et al., 2014; Glahn et al., 2010) (N = 118; N = 557; N = 371) as not (Civil Arslan et al., 2014; Deveci et al., 2013; Kulkarni et al., 2010) (N = 55; N = 30; N = 30).

Performance in this domain among relatives was also mixed using the Stop Signal Task (SST) and the Hayling Sequence Completion Task (HCST). Notably, Fears et al. (2014)(N = 557) found that inhibitory control, as measured by the number of correct Go trials in the SST, was associated with BD, but was not heritable. Conversely, this same domain, as measured by the number of correct Stop trials in the SST, was neither heritable, nor associated with BD. Likewise, performance on the HSCT was similar to (Christodoulou et al., 2012; Deveci et al., 2013) or lower than (Schulze et al., 2011) that of healthy controls. While there appears to be a clear deficit in response inhibition among *patients*, this association is less consistent in *relatives* of BD.

2.2.2. Cognitive set-shifting—Twenty-one studies evaluated cognitive set shifting in *patients* (14 studies) and *relatives* (7 studies) using the Wisconsin Card Sorting Test (WCST). This subdomain was impaired in the majority of measures among *patients with BD* (15/24), whereas among relatives it was more often than not preserved (6/11 measures). The number of categories completed in the WCST among patients was similar to (Martinez-Aran et al., 2009, 2007; Torrent et al., 2006, 2011) or lower than that completed by controls (Ancin et al., 2013; Bonnin et al., 2012; Elshahawi et al., 2011; Marshall et al., 2012; Santos et al., 2014). Likewise, the percentage of perseverative errors committed by *patients* was also similar to (Bonnin et al., 2012; Martinez-Aran et al., 2007; Martino et al., 2011a; Torrent et al., 2006, 2011) or lower than that committed by controls (Ancin et al., 2013; Bonnin et al., 2012; Elshahawi et al., 2011; Marshall et al., 2012; Martinez-Aran et al., 2009; Martino et al., 2014; Ryan et al., 2013; Sanchez-Morla et al., 2009; Santos et al., 2014). Cognitive set shifting impairment as measured by perseverative errors and categories completed was also observed in *relatives* (Civil Arslan et al., 2014; Rabie and Rami, 2009). However, the majority of *relative* studies observed similar performance to controls in categories (Deveci et al., 2013; Kulkarni et al., 2010; Maziade et al., 2009) and, to a lesser extent, in perseverative errors (Erol et al., 2014; Kulkarni et al., 2010). Thus, although evidence points towards moderate deficits in this domain among *patients with BD*, there is no consistent evidence of impairment among *relatives*.

2.2.3. Planning—Preliminary findings indicate planning deficits among both *patients with BD* and *relatives*. Deficits were found among *patients* using the Tower of Hanoi task (Ancin et al., 2013; Dias et al., 2008) (N = 148; N = 70) and the D-KEFS Tower Test (Palsson et al., 2013) (N = 110); as well as in *unaffected first-degree relatives* using the Tower of London test (Kulkarni et al., 2010) (N = 30).

2.2.4. Abstract reasoning—This function was assessed in three studies of *relatives*, using five tasks. Abstract reasoning was preserved in *relatives* by the WASI Matrix Reasoning subtest (Fears et al., 2014; Glahn et al., 2010), the Test of Nonverbal Intelligence, the Abstraction, Inhibition, and Working Memory Task (Fears et al., 2014), and the Intradimensional/Extradimensional Shift from the CANTAB (Schulze et al., 2011). Although abstraction and concept formation impairment was found in one study with the Penn Conditional Exclusion Test (Glahn et al., 2010) (N = 371), no such impairment was found in other studies (Fears et al., 2014) (N = 557). Thus, there is no consistent evidence of impaired abstract reasoning in *relatives* of patients with BD.

2.3. Attention

This domain was evaluated in 34 studies among *patients with BD* (22 studies) and *relatives* (12 studies) using thirteen different tests. Attention was highly impaired in *patients* (39/40 tasks) and less so in *relatives* (12/22 tasks).

2.3.1. Sustained attention—Eleven studies evaluated this function using two different tests among *patients* (4 studies) and *relatives* (8 studies). Sustained attention was impaired in all 4 measures among *patients* and in 5 out of 8 measures among *relatives*. Malloy-Diniz et al. (2011) found deficits among *patients* on the Continuous Performance Test-II (CPT-II). In addition, several studies found that *patients* had fewer correct responses to stimuli (Sanchez-Morla et al., 2009; Santos et al., 2014) and a longer reaction time and lower sensibilities a and d' in all blocks (Ancin et al., 2010), than healthy controls on the Degraded Stimulus-CPT (DS-CPT). These result suggest that variants of the CPT task may detect deficits in sustained attention in both *patients* and *relatives*.

2.3.2. Visual attention & task switching—Twenty-three studies among *patients with BD* (16 studies) and *relatives* (7 studies) evaluated this function using the Trail Making Test-Part A (TMT-A). This function was impaired in all 16 studies among *bipolar participants*, and in fewer than half of studies (3/7) among *relatives*. However, one report found that the BDI group's performance was no different from that of controls, but the BDII group demonstrated a deficit in the same task (Martino et al., 2011b). Fifteen studies report dysfunction among BDI (Brissos et al., 2011; Dias et al., 2008; Santos et al., 2014) and both BDI and BDII *patients* (Ancin et al., 2013; Bonnin et al., 2012; Dittmann et al., 2008; Elshahawi et al., 2011; Marshall et al., 2012; Martinez-Aran et al., 2009, 2007; Martino et al., 2011a,b; Ryan et al., 2013; Santos et al., 2014; Torrent et al., 2006, 2011). Notably, results among *relatives* were mixed: some studies reported performance similar to controls (Antila et al., 2011; Civil Arslan et al., 2014; Kulkarni et al., 2010) on the TMT-A, while other studies reported lower performance (Antila et al., 2009; Deveci et al., 2013; Erol et al., 2014; Glahn et al., 2010). Therefore, while the TMT-A consistently measured deficits in *patients*, there is no consistent evidence that *relatives* are impaired in visual attention as measured by the TMT-A.

2.3.3. Attentional Control/Impulsivity—This function was assessed in three studies using the Iowa Gambling Test among *patients* (2 studies) and *relatives* (1 study). Two studies found a deficit among *patients* (Adida et al., 2011; Malloy-Diniz et al., 2011). No deficits were found among *unaffected first-degree relatives* (Kulkarni et al., 2010).

2.3.4. Attention and concentration—This function was assessed in nine studies among *patients with BD* using the WAIS and WMS versions of the Digit Span Test-Forward (DST-F) and Backward (DST-B). This function was impaired among bipolar participants in the majority of studies (15/16) and in half of the studies of relatives (2/4). Among ten studies testing DST-F, the majority found significant deficits among *patients* (Bonnin et al., 2012; Brissos et al., 2011; Dias et al., 2008; Martinez-Aran et al., 2009, 2007; Martino et al., 2011a, 2014; Torrent et al., 2006, 2011); only one report found comparable scores between healthy controls and BDI or BDII groups (Martino et al., 2011b). Similarly, six studies

testing DST-B all demonstrated poorer performance among *bipolar participants* (Bonnin et al., 2012; Brissos et al., 2011; Dias et al., 2008; Martinez-Aran et al., 2009, 2007; Torrent et al., 2011). While there is consistent evidence of impaired attention and concentration among *patients*, functioning in this domain among *relatives* remains unclear.

2.4. Memory

Sixteen studies evaluated several memory functions using nine different tests in *patients with BD* (20 studies) and *relatives* (13 studies), not accounting for subtests. The broad domain of memory was mostly impaired in *patients* (66/92 measures), and only marginally impaired in *relatives* (40/78 measures).

2.4.1. Verbal learning & memory—This function was assessed in twenty-eight studies among *patients with BD* (17 studies) and *relatives* (11 studies) using the several tests. *Patients* were impaired in most tasks assessing this domain (49/70). *Relatives* were also impaired, although not as often (19/36 measures). Two studies reported similar performance between *patients* and healthy controls in immediate and delayed recall, list learning, and recognition tasks (Bonnin et al., 2012; Ryan et al., 2013). Among twelve studies that tested immediate and delayed recall, 10 studies demonstrated poorer performance among *patients* using the California Verbal Learning Test (CVLT) (Bonnin et al., 2012; Martinez-Aran et al., 2009, 2007; Sanchez-Morla et al., 2009; Santos et al., 2014; Simonsen et al., 2011; Torrent et al., 2006), the Wechsler Memory Scale (WMS) Logical Memory task (Bonnin et al., 2012; Simonsen et al., 2011), and the Memory Battery of Signoret (MBS) (Martino et al., 2011a,b, 2014). *Patients with BD* also performed poorly on the recognition subtest of the CVLT (Martinez-Aran et al., 2009, 2007; Sanchez-Morla et al., 2009; Torrent et al., 2006, 2011). Performance for list learning, tested in twelve studies, showed a similar pattern, with nine studies showing significant deficits with the CVLT (Bonnin et al., 2012; Martinez-Aran et al., 2009, 2007; Sanchez-Morla et al., 2009; Santos et al., 2014; Simonsen et al., 2011; Torrent et al., 2006, 2011). Thus, substantial evidence points towards significant deficits in verbal learning and memory among *patients* particularly when using the CVLT.

On the other hand, *relatives* appeared to have preserved functioning in this domain when tested with the CVLT (6/23 measures). Deficits in verbal learning and memory were only consistently detected when *relatives* were tested using the RAVLT (7/10 measures). Although both the CVLT and the RAVLT require the participant to learn lists of words over five acquisition trials and then recall them after an interference trial, the list of 16 words in the CVLT permits semantic clustering, which may facilitate word recall, whereas the list of 15 words in the RAVLT does not. Additionally, others have suggested that besides verbal learning, the CVLT also relies on executive functioning (Tremont et al., 2000) which is consistently impaired among bipolar patients and modestly among relatives.

Six studies found significant impairments in delayed recall with the CVLT (Antila et al., 2009; Fears et al., 2014; Maziade et al., 2009) or the RAVLT (Deveci et al., 2013; Kulkarni et al., 2010). However, four studies evaluating this function also using the CVLT (Antila et al., 2011; Drysdale et al., 2013; Glahn et al., 2010) and the RAVLT (Civil Arslan et al., 2014) failed to find this association. Results were even more mixed for immediate recall,

with three studies reporting deficits with the CVLT (Drysdale et al., 2013) or RAVLT (Deveci et al., 2013; Kulkarni et al., 2010), and three other studies reporting no deficits (Antila et al., 2011, 2009; Civil Arslan et al., 2014). *Relatives* were impaired in recognition tasks according to three studies with the CVLT (Antila et al., 2009) or RAVLT (Civil Arslan et al., 2014; Deveci et al., 2013), but not in four other studies (Antila et al., 2011; Drysdale et al., 2013; Fears et al., 2014; Maziade et al., 2009). List learning was impaired in seven studies using the RAVLT and CVLT (Antila et al., 2009; Civil Arslan et al., 2014; Deveci et al., 2013; Fears et al., 2014; Glahn et al., 2010; Kulkarni et al., 2010; Maziade et al., 2009), with the exception of two studies using the CVLT (Antila et al., 2011; Drysdale et al., 2013). Thus there is some consistent evidence that relatives are impaired in this domain, especially when tested with the RAVLT.

2.4.2. Visual-spatial learning & memory—Eleven studies assessed this function in *patients* (6 studies) and *relatives* (5 studies) using several tasks. *Patients with BD* were impaired in all five measures assessing this function, whereas *relatives* were less impaired (6/16 measures). Specifically, *patients* (Ryan et al., 2013; Sanchez-Morla et al., 2009; Santos et al., 2014) and *relatives* (Doyle et al., 2009; Kulkarni et al., 2010; Maziade et al., 2009) both showed deficits in delayed and immediate recall in the Rey-Osterrieth Complex Figure Test (ROCFT), and in immediate recall, Rey figure drawing, and recognition tasks in a Delis-Kaplan Executive function system (D-KEFS) version of the ROCFT (Palsson et al., 2013). Only one study among *first-degree relatives* failed to find deficits in a visual recognition task with a variant of the ROCFT (Maziade et al., 2009). Various other tasks of visual learning and memory point toward preserved functioning in this domain among relatives, however none were assessed consistently. Overall, there is preliminary evidence for impaired visuospatial functioning in patients, but not among *relatives*.

2.4.3. Episodic memory—This function was assessed in only five studies among *patients with BD* (1 study) and *relatives* (4 studies) using the Claeson-Dahl task Verbal episodic memory (Palsson et al., 2013), the Penn Face Memory Test (facial episodic memory) (Fears et al., 2014; Glahn et al., 2010), or the Verbal Paired Associates Test (explicit verbal episodic memory) (Rabie and Rami, 2009). Among *relatives* this function was impaired in all four studies assessing this domain, whereas among BDI & BDII patients this function was preserved by the Claeson-Dahl test (Palsson et al., 2013) (N = 110). Specifically significant deficits in this domain were found among large samples of *relatives* (n = 557, 371, and 85) in the delayed and immediate memory conditions of the Penn Face Memory Task (Fears et al., 2014; Glahn et al., 2010) and the Verbal Pairs Associates Test (Rabie and Rami, 2009). Although fewer studies have tested episodic memory among both *patients* and *relatives* there may be sufficient preliminary evidence to indicate that this subdomain may be impaired at least in *relatives* of Patients with BD.

2.4.4. Working memory—Verbal working memory was assessed in eighteen studies among *patients with BD* (10 studies) and *relatives* (8 studies) using several tasks. *Bipolar* participants showed more consistent impairment in this domain (12/16 measures) than relatives (10/21 measures).

Specifically, the majority of studies found impaired working memory in *patients* using the Digit Span Test-Backward (DST-B) (Ancin et al., 2013; Elshahawi et al., 2011; Martino et al., 2014; Sanchez-Morla et al., 2009; Simonsen et al., 2011), with one exception (Santos et al., 2014). In contrast, among *relatives* only one study found deficits with the DST-B (Glahn et al., 2010), whereas the majority of studies found no deficits (Antila et al., 2011, 2009; Deveci et al., 2013; Fears et al., 2014; Schulze et al., 2011). *BD patients* with single or recurrent manic episodes (Elshahawi et al., 2011) and BDI and BDII *patients* (Ancin et al., 2013) both showed significant deficits using the Digit Span Test-Forward (DST-F). Two *relative* studies using DST-F also reported deficits (Deveci et al., 2013; Glahn et al., 2010). However, other studies among *relatives* failed to find this association (Antila et al., 2011, 2009; Deveci et al., 2013; Fears et al., 2014) using this same task. These results suggest that the DST-F and DST-B consistently measure impaired working memory among *patients*, but not among their *relatives*.

Two large scale studies using different measures, namely the Letter Number Sequencing task (LNST) and the Spatial Delayed Response Task found working memory deficits among *first*- and second-degree relatives as well as bipolar patients (Fears et al., 2014; Glahn et al., 2010). This suggests that different measures may be capturing different aspects of working memory.

2.4.5. Processing speed—Eleven studies assessed this function in *patients with BD* (5 studies) and *relatives* (6 studies) using the Wechsler Adult Intelligence Scale (WAIS) Digit Symbol Coding task. The majority of studies observed significant deficits in *patients* (Marshall et al., 2012; Ryan et al., 2013; Santos et al., 2014; Simonsen et al., 2011) and *relatives* (Antila et al., 2011, 2009; Daban et al., 2012; Fears et al., 2014; Glahn et al., 2010), with one exception (Doyle et al., 2009). Additionally, two large studies found that processing speed as measured by Digit Symbol Coding task was also heritable and significantly associated with BD suggesting that the Digital Symbol task may be sensitive to capturing deficits that are familial (Fears et al., 2014; Glahn et al., 2010).

2.5. Verbal fluency

This function was evaluated among *patients with BD* (17 studies) and *relatives* (8 studies) using three measures. Verbal fluency impairments were found both among patients (26/32 measures) and *relatives* (7/11).

2.5.1. Phonemic fluency—Eleven studies found deficits among patients on phonemic fluency measured with the FAS, Phonological Fluency task, or Letter Fluency task (Ancin et al., 2013; Bonnin et al., 2012; Marshall et al., 2012; Martinez-Aran et al., 2009, 2007; Martino et al., 2011a,b, 2014; Palsson et al., 2013; Ryan et al., 2013; Sanchez-Morla et al., 2009; Santos et al., 2014; Simonsen et al., 2011; Torrent et al., 2006, 2011), although five studies failed to find significant deficits (Bonnin et al., 2012; Martinez-Aran et al., 2007; Martino et al., 2011b; Torrent et al., 2006). Similarly, among *relatives* four studies found significant impairment in performance on phonemic fluency measured with the VFT and D-KEFS Letter Fluency (Glahn et al., 2010; Maziade et al., 2009) or the COWA/T FAS(Christodoulou et al., 2012; Deveci et al., 2013), whereas two studies using the same

tasks found no such impairment (Drysdale et al., 2013; Fears et al., 2014). Overall, preliminary evidence shows that phonemic fluency may be impaired in *patients*, but evidence for impairment among *relatives* is less consistent.

2.5.2. Semantic fluency—Thirteen studies found significant deficits among *patients* with the COWA/T and D-KEFS Animal Naming Fluency. Only two studies, using the Semantic Fluency task (Martino et al., 2011b) or the COWA/T Animal Naming Fluency task (Dias et al., 2008), failed to find deficits. Among *relatives*, five studies found significant impairment in semantic fluency using the D-KEFS Category/Animal Naming task (Fears et al., 2014; Glahn et al., 2010) or the VFT (Drysdale et al., 2013; Maziade et al., 2009), but one study failed to detect impairment (Erol et al., 2014). Thus evidence from various studies suggests that semantic fluency deficits as measured by the COWA/T and the D-KEFS, can be found among both *patients* and *relatives*.

2.6. Social cognition & emotion processing

These functions were evaluated in nine studies among *patients with BD* (3 studies) (N = 237; N = 156; N = 36) and *relatives* (6 studies) using fifteen different tests. Social cognition and emotion processing were impaired as measured by only a few tasks (3/10) among *patients*, but by the majority of measures among *relatives* (6/8). Although fewer studies have tested social cognition and emotion processing among *patients* and *relatives*, there may be sufficient preliminary evidence to indicate that this subdomain may be impaired at least in *relatives* of BD patients. However, since no task was measured by more than two studies further work will be needed to explore this potential association. It is worth noting that further studies assessing this domain in BD patients may have had sample sizes below our cut-off score (N > 68) and were therefore excluded from this review.

3. Discussion

This study provides an updated qualitative review of neuropsychological impairment in euthymic BD patients *and* individuals at familial risk for developing BD. It includes studies published since the last major meta-analyses (Arts et al., 2008; Bora et al., 2009). In addition to identifying those domains affected among both BD patients and at-risk relatives, the current review identifies specific instruments most sensitive to detecting cognitive deficits in both groups. We have reviewed results from among the most robust findings available to date by including studies with larger sample sizes, appropriate controls, and documentation of current mood state.

Our findings regarding neurocognitive deficits found in bipolar patients were broadly similar to those of a recent meta-analysis that analyzed 31 primary data sets as a single large sample (N = 2876). Both articles found impairments in intelligence, verbal learning and memory, executive functioning, response inhibition, attention/working memory, set shifting, and processing speed. Our findings were in line with Bourne et al. (2013) identification of the Verbal Learning Tests, Digit Span Test, and the Trail Making Test as the most robust measures of cognitive impairments in bipolar disorder patients. Notably these tasks all appear in the ISBD's proposal for a consensus based battery (Yatham et al., 2010).

We found several studies that reported neurocognitive impairment in both patients and relatives. Deficits in verbal fluency, verbal learning/memory, attention, and processing speed were most prominent. In contrast, unaffected relatives usually appeared to have preserved intelligence, working memory, and visual-spatial learning/memory. These results are in line with prior findings from meta-analytic reviews (Table 5). This review also identified those instruments showing the highest magnitude of impairment among patients with BD and relatives: executive functioning (Stroop Color Word Test, Wisconsin Card Sorting Test), attention (Continuous Performance Test & variants), processing speed (Wechsler Adult Intelligence Scale-Digit Symbol Coding), verbal learning and memory (Rey's Auditory Verbal Learning Test), and visual-spatial learning and memory (Rey-Osterrieth Complex Figure Test).

There are several important methodological limitations. Because of the wide variety of measures used to assess cognitive functioning and the differences in selection criteria across studies, we chose to provide a qualitative summary of the literature rather than a quantitative meta-analysis. This approach limits the ability to account for sampling differences due to ascertainment and sample size that may contribute to some of the discrepant findings we report across studies. Notably, the studies of high-risk *relatives* had smaller sample sizes (median N = 28) than the *patient* studies (median N = 100). Since smaller sample sizes can under or overestimate effect sizes, this may contribute to the greater frequency of inconsistent findings we observed across the studies of relatives.

Another methodological limitation results from differences across studies in controlling for variables that may affect performance on neuropsychological tests. Some of the most important differences will be discussed here. Studies differed in their definition of euthymia, even though many cognitive measures are highly sensitive to current mood state (Malhi et al., 2007; Martinez-Aran et al., 2004; Quraishi and Frangou, 2002). Studies also differed in their exclusion criteria for mental illness among relatives. Some studies included relatives with a lifetime history of anxiety, ADHD, disruptive behavior disorder, or major depressive disorder (e.g., (Allin et al., 2010; Thermenos et al., 2010), for example, which could contribute to neuropsychological deficits independent of the genetic risk for BD. Studies also differed in the information provided regarding how closely related family members were to the identified patient with BD. The majority of the studies we reviewed included first-degree relatives, who are at substantial lifetime risk for developing BD (5–10%) (Craddock and Jones, 1999), while others included second-degree relatives whose lifetime risk for BD (0.5–1.5%) is comparable to that seen in the general population (Gershon et al., 1982; Smoller and Finn, 2003). Some apparent cognitive deficits in unaffected relatives could actually represent prodromal symptoms preceding illness, but only a handful of studies controlled for subclinical depressive or manic symptoms e.g., (Brand et al., 2012; Quraishi et al., 2009). Deficits might also represent environmental risk factors shared with the affected relative, such as socioeconomic disadvantage or other adversity.

Why do some at-risk relatives seem to show more pronounced neurocognitive deficits than others? All at-risk relatives may not share similar risk factors. Even close relatives may differ in their genetic risk. For example, siblings may share anywhere from 25% to 75% of inherited genes (Visscher et al., 2006) and rarely share any de novo events such as copy

number variants or point mutations that may contribute substantially to cognitive performance (Georgieva et al., 2014; Iossifov et al., 2012). Siblings may also differ in their health, life experiences, and other non-genetic factors that could influence neurocognitive performance. Most high-risk studies rely on comparisons between relatives of patients and unrelated controls, which may not be well matched on genetic background.

In a study of deletions on chromosome 16p, Moreno-De-Luca et al. (2015) demonstrated a study design involving family controls, where affected and unaffected offspring can be compared not with unrelated controls but with expectations based on the average performance of their unaffected parents across a range of neuropsychological domains. This design works best for measures that are not very sensitive to age, but could be adapted to "high-risk" studies undertaken in the absence of an identified genetic risk factor.

More research is needed on the identification of cognitive measures used for the prediction of BD illness onset including in-depth research of individuals at familial risk. In its current state, neuropsychological testing and family history have very limited predictive validity (Olvet et al., 2013). Future studies might benefit from direct measures of genetic and environmental risk factors shared by patients and individuals at familial risk. Polygenic risk scores provide one way to assess genetic risk, but account for only a small portion of the variance in risk for illness and are often strongly cor-related among close relatives (Fullerton et al., 2015). Non-genetic risk factors, such as head injury, are rarely assessed but could play an important contributory role (Chi et al., 2015; Deb et al., 1999; Jorge and Robinson, 2003). Biomarkers could offer additional precision. For example, functional magnetic resonance imaging (fMRI) research using face emotion and attentional tasks has found evidence of dysfunction in limbic and prefrontal regions that is present in patients with BD and in their unaffected relatives (Brotman et al., 2014; Kim et al., 2012; Olsavsky et al., 2012; Singh et al., 2014; Surguladze et al., 2010; Tseng et al., 2015).

Another limitation is the absence of longitudinal studies. While cross-sectional studies provide useful information, by conducting longitudinal studies of high-risk first-degree relatives of patients with BD we may be able to determine whether deficits are present prior to the onset of the illness or whether they develop subsequent to its onset. The former would suggest that a neurodevelopmental model might best explain the presence of cognitive deficits in first-episode BP patients (FEBP), whereas the latter might suggest a neurodegenerative model is at play. Notably, no support for a neurodegenerative model has been found in longitudinal studies of recently diagnosed bipolar patients (Torres et al., 2014) and first-episode BD (Bombin et al., 2013). Furthermore, the hypothesis that allostatic load may play a role in neurocognitive decline is similarly not supported by the more recent longitudinal reviews of recently diagnosed BD patients or by the fact that cognitive decline is seen, albeit to a lesser extent and less consistently, in relatives without the illness (Vieta et al., 2013). In fact, according to two recent reviews (Bora, 2015; Lee et al., 2014), neurocognitive deficits are already present in first-episode bipolar patients. Together these findings suggest that cognitive deficits cannot be explained by mood symptoms and that a neurodevelopmental model may best explain the presence of cognitive deficits in FEBP.

To complicate matters further, investigations into premorbid cognitive functioning have led to conflicting results. According to various studies, both premorbid cognitive impairment (Tiihonen et al., 2005) and above average premorbid cognitive abilities seem to be risk factors for developing BD (Cannon et al., 1997). Bora (2015) argues that low sample size and poor study design may explain some of these conflicting findings.

In sum, we have sought to provide an updated review of findings from prior research assessing neurocognitive domains in patients with BD and in unaffected relatives. We have found that different measures consistently detect impairment in patients, however, not so when looking at unaffected relatives. We have discussed some of the methodological and conceptual issues that may contribute to the inconsistent findings, especially small sample sizes and wide variation in the choice of neurocognitive measures. The widespread adoption of a consensus-based battery would lead to easier synthesis and assessment of available findings across future studies.

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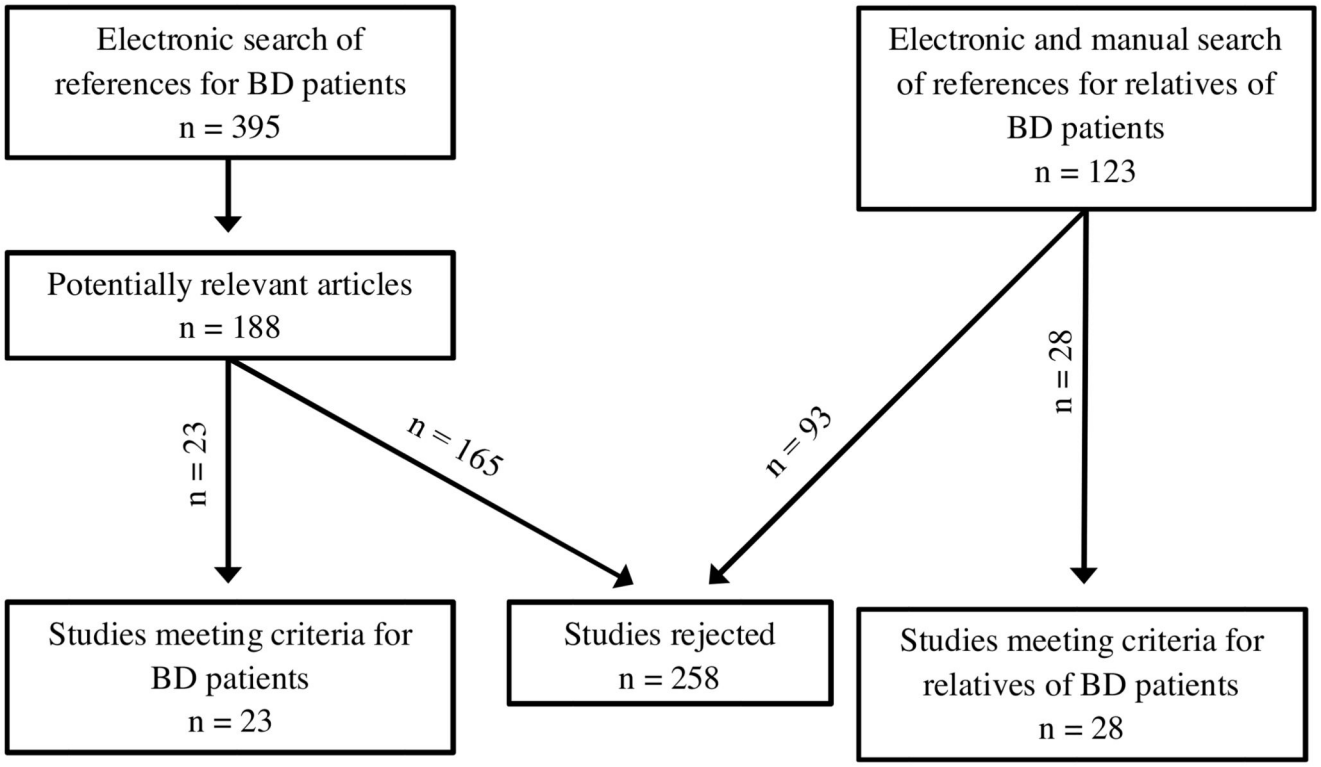

Fig. 1.
Flow chart of study selection for the systematic review.

Table 1

Summary of BD patient study sample and euthymia criteria.

	Primary Study	Sample	Criteria of euthymia
1	Torrent et al. (2006)	71 BD (38 BDI 33BDII) 35 HC	YMRS ≤ 6, HDRS ≤ 8 During monthly visits over 6-month period
2	Martinez-Aran et al. (2007)	77 BDI & BDII (31 LF & 46 HF) 35 HC	YMRS ≤ 6, HDRS ≤ 8 During monthly visits over 6-month period
3	Dias et al. (2008)	70 BDI (45 BD-IN & 25 BD-PI) 50 HC	YMRS ≤ 6, HDRS ≤ 7
4	Dittmann et al. (2008)	103 BD (65 BDI 38 BDII) 62 HC	YMRS ≤ 5, HDRS ≤ 8\ At least one month prior to testing
5	Martinez-Aran et al. (2009)	103 BDI & BDII (61 GTC & 42 PTC) 35 HC	YMRS ≤ 6, HDRS ≤ 8 During monthly visits over 6-month period
6	Sanchez-Morla et al. (2009)	73 BD (55 BDI 18BDII) 67 HC	YMRS(Spanish)≤ 6, HDRS (Spanish) ≤ 7 During 3 month period
7	Ancin et al. (2010)	141 BDI & BDII 105 HC	YMRS ≤ 6, HDRS ≤ 7 During monthly visits over 3-month period
8	Adida et al. (2011)	167 BDI (90 Euthymic) 150 HC	YMRS ≤ 8, HDRS ≤ 8
9	Brissos et al. (2011)	30 HPS− BDI 44 HPS+ BDI 50 HC	YMRS ≤ 6, HDRS ≤ 8 At least one month prior to testing
10	Torrent et al. (2011)	84 BDI & BDII 35 HC	YMRS ≤ 6, HDRS ≤ 8 During monthly visits over 6-month period
11	Elshahawi et al. (2011)	100 BDI & BDII (50 First Episode 50 recurrent episode) 50 HC	YMRS ≤ 6, HDRS ≤ 8 During 3 month period
12	Malloy-Diniz et al. (2011)	95 BD 94 HC	YMRS < 13, Beck < 12
13	Martino et al. (2011a,b)	81 BD (45 BDI 36BDII 34 HC	YMRS ≤ 6, HDRS ≤ 8 During 2 month period
14	Martino et al. (2011a,b)	87 BD (48 BDI 39 BDII) 39 HC	YMRS ≤ 6, HDRS ≤ 8 During 2 month period
15	Simonsen et al. (2011)	27 SA 136 BD I & II (75 HPS+ & 61 HPS−) 280 HC	YMRS, IDS-CR.
16	Torrent et al. (2012)	69 BD (53 BDI 15 BDII) 45 HC	YMRS ≤ 6, HDRS ≤ 8 During monthly visits over 6-month period
17	Bonnin et al. (2012)	103 BDI & BDII (57 Subsyndromal & 46 Asymptomatic) 30 HC	YMRS ≤ 6, HDRS ≤ 8 At least 6 months prior to testing
18	Marshall et al.(2012)	201 BDI 36 BDII 19 BPNOS (158 SUD+ BDI & II 98 SUD− BDI & II) 97 HC	YMRS ≤ 7, HDRS
19	Ancin et al. (2013)	148 BD (118 BDI 30 BDII) 108 HC	YMRS < 6, HDRS < 7
20	Palsson et al. (2013)	110 BD (67 BDI 43 BDII) 86 HC	YMRS ≤ 14, MADRS ≤ 14 At least 3 consecutive months prior to testing
21	Ryan et al. (2013)	133 BDI & 23 BDII (123 working, 33 not working) 143 HC (125 working, 18 not working)	YMRS < 8, HDRS < 8 At time ofneuropsychological testing
22	Martino et al. (2014)	100 BDI & BDII 40 HC	YMRS < 8, HDRS < 9 At least two months prior to testing
23	Santos et al. (2014)	80 BD 40 HC	YMRS < 6, HDRS < 7 At least the previous 3 months

BDI: Bipolar Disorder I. BDII: Bipolar Disorder II. HC: Healthy Control. YMRS: Young Mania Rating Scale. HDRS: Hamilton Depression Rating Scale. LF: Low functioning. HF: High Functioning. II: Bipolar Disorder with impaired insight. PI: Bipolar Disorder with preserved insight. GTC: Bipolar Disorder with good treatment compliance. PTC: Bipolar Disorder with poor treatment compliance. HPS−: BD patient without history of psychotic symptoms. HPS+: BD patient with history of psychotic symptoms. Beck: Beck Depression Inventory. SA: Schizoaffective. IDSCR: Inventory of Depressive Symptoms-Clinical Rating. SUD+: History of substance abuse. SUD−: No history of substance abuse. MADRS: Montgomery-Åsberg depression rating scale.

Table 2

Key findings of studies with relatives of bipolar disorder patients.

Study	Sample	Tests	Main results		Commentaries	
Brotman et al. (2008)	25 BD-RL (UFDR) 37 BD 36 HC	EEMT, WASI (IQ)	-	BD = BD-RL < HC: EEMT	-	Age Range:7–18 years old
			-	BD < HC: IQ	-	BD-RL had parent (n = 11) or sibling (n = 14) with BD and history ofanxiety disorders or ADHD
			-	BD-RL = HC: IQ		
Brotman et al. (2008)	24 BD-RL (UFDR) 52 BD 78 HC	DANVA, WASI, DAS	-	BD = BD-RLs < HC: DANVA	-	Age Range: 4–18 years old.
			-	BD < HC < BD-RL: WASI, DAS	-	BD-RLs :history of anxiety disorder and ADHD
					-	BD-RLs were medication free
					-	Sample not completely independent from McClure et al. (2005)
Brotman et al. (2009)	26 BD-RL (UFDR) 28 BD 24 HC	FCPT, WASI (FSIQ)	-	BD & BD-RLs > HC: ISV-RT	-	Age Range: 7–17 years old.
			-	BD = BD-RL = HC: FSIQ	-	History of anxiety and disruptive behavior disorders, and ADHD among BD-RLs
					-	52% of pediatric BDs were euthymic
Quraishi et al. (2009)	49 BD-RL (UFDR) 38 BD 44 HC	WAIS-R (Vocabulary, Comprehension, Similarities, Block Design, Object Assembly, FSIQ), WMS (LMT, VR, PAL)	-	BD-RL < HC: WAIS-R (Comprehension, Similarities), PAL(verbal learning), LMT (immediate & delayed verbal memory)	-	BD had BDI with history of psychotic symptoms
					-	20% of BD-RLs had lifetime diagnosis of non-psychotic, non-bipolar Axis I diagnosis
			-	BD-RL = HC: VR: (immediate & delayed), FSIQ, Object Assembly, Block Design, Vocabulary	-	BD-RLs from multiply affected families
Antila et al. (2009)	64 BD-RL (UFDR) 39 BD 55 HC	WAIS-R (Vocabulary, DSC), WMS-R (DST-F, DST-B, VS-F, VS-B CVLT(delayed, immediate recall, learning trials, interference, recognition,	-	BD-RLs from bipolar families = BD-RLs from mixed family.	-	Bipolar family and mixed family sample (BD & SABP or Schizophrenia) were studied separately: 20 BDI & 36 BD-RLs
			-	Bipolar family BD-RLs < HC: (DSC, TMT-B)		

Study	Sample	Tests	Main results		Commentaries	
		semantic clustering, TMT-A, TMT-B	-	Mixed family BD-RLS < HC: (DSC)		from bipolar family; 19 BDI & 28 BD-RLs from mixed families.
			-	Bipolar family & Bipolar mixed family = HC: WAIS-R (Vocabulary)	-	19 BD-RLs had a lifetime psychiatric disorder.
			-	BD from bipolar families = BD from mixed family.	-	HCs not independent from Antila et al. (2007) and Antila et al. (2007)
					-	17 HCs had lifetime Axis I diagnosis (not current, except for specific phobia) and no family history of psychopathologies
Doyle et al. (2009)	118 BD-RL (UFDR) 170 BD 79 HC	WISC-III/WAIS-III(Arithmetic, DST, DSC, Symbol Search, FSIQ (Vocabulary & Block Design), SCWIT, WCST, ROCF, CVLT, Seidman WM INT CPT)	-	BD-RLs < HC: abstract problem solving (WCST Perseverative & non-perseverative errors, ROCF), Seidman WM INT (CPT)	-	Used logistic regression analyses to assess association between group status and performance on three factor scores (Factor 1: processing speed/ verbal learning; Factor 2: Working memory/ interference control; Factor 3: Abstract problem solving)
			-	BD-RLs = HC (DSC, SCWIT, CVLT)		
			-	BD < HC & BD-RL: FSIQ, although all scored within average range.		
					-	Not independent from Wilens et al. (2004) and Wozniak et al. (2005)
Maziade et al. (2009)	23 BD-RL (UFDR) 45 HC	WISC-III/WAIS-III (FSIQ), CPT-II, CVLT, RCFT, DST, Corsi, WCST, VFT, TOL, Purdue Pegboard	-	BD-RL < HC: FSIQ, CPT, CVLT (total recall, delayed recall), RCFT (immediate and delayed recall), Corsi, WCST (total errors),VFT (category & letter fluency), TOL	-	Targeted multigenerational families densely affected by BD or Schizophrenia in Eastern Quebec.
					-	Mean age of BD-RLs: 17.45
			-	BD-RL = HC: CVLT (recognition), RCFT (recognition), DST, WCST (categories), Purdue pegboard		
Rabie and Rami (2009)	85 BD-RL 50 HC	WAIS (Similarities, Block Design), WMS-R (VPA, DST,	-	BD-RL > HC: WAIS	-	Participants with current or history of psychiatric

Study	Sample	Tests	Main results		Commentaries	
		VS), WCST		(similarities & Block Design)		disorders were excluded
			-	BD-RL < HC: DST, VS, VPA (delayed & immediate recall), WCST (Categories & perseverative errors)		
Allin et al. (2010)	20 BD-RL (UFDR) 20 BD 20 HC	VFT (easy & hard conditions)	-	BD < HC & BD-RL: Easy condition	-	Did not exclude relatives or controls with lifetime history of psychiatric disorders other than psychosis or BD
			-	BD = BD-RL = HC: Hard condition		
Glahn et al.(2010)	371 BD-RL 230 BD 108 HC	PCET, IP-CPT, TMT-A, TMT-B, SCWT, WAIS-III (DSC, DST-F& DST-B), ODRT, LNST, SDRT, PFMT, CVLT, D-KEFS (letter and category fluency), WASI (Matrix Reasoning)	-	BD-RLs < HC: PCET, IP-CPT, TMT-A, TMT-B, SCWT, LNST, WAIS-III (DST-F & DST-B), SDRT, PFMT (delayed facial memory), CVLT (Total Trials 1–5, but not semantic cluster or delayed recall), D-KEFS letter and category fluency); Heritable, but not genetically correlated with affection status	-	Recruited families with at least two siblings with BD diagnosis
					-	161 BDI; 51 BDII; BD 6 NOS; 12 SABD; 243 UFDR; 128 USTDR
					-	Assessment took place in Costa Rica, San Antonio, & Mexico City
			-	BD-RL = HC: Matrix Reasoning		
			-	BD-RL < HC: WAIS-III (DSC), ODRT, PFMT(immediate facial memory), (includes BD broad/relatives); Heritable, associated with BD, and significantly genetically correlated with illness risk		
Kulkarni et al. (2010)	30 BD-RL (UFDR) 30 HC	CPT, TMT-A,TMT-B, SCWIT, TOL, IGT,WCST (categories & perseverative error),RCFT, RAVLT	-	BD-RL = HC: CPT, TMT-A, TMT-B, SCWIT, WCST (categories & perseverative errors), IGT	-	Participants were not on any medication affecting cognition
					-	UFDR had 2+ BD family members
			-	BD-RL < HC: TOL, RCFT(delayed recall), RAVLT (total learning, immediate and		

Study	Sample	Tests	Main results		Commentaries	
				delayed word recall)		
Kumar et al. (2010)	88 BD-RL (UFDR) 47 BD 93 HC	WAIS-R (FSIQ), DS-CPT	-	BD & BD-RL = HC: DS-CPT, IQ	-	Sample has high history of psychosis
					-	36 BD prescribed antipsychotics
					-	25 BD received mood stabilizers
Surguladze et al. (2010)	20 BD-RL (UFDR) 20 BD 20 HC	"Facial expressions of emotion: stimuli and tests"	-	BD-RL & BD > HC: greater brain activation to both fearful and happy faces	-	Lifetime history of non-psychotic, psychiatric symptoms was not an exclusion factor for BD-RLs
					-	Participants described in Drapier et al. (2008)
Thermenos et al. (2010)	18 BD-RL (UFDR) 19 BD 19 HC	WAIS-R (Vocabulary & Block Design) WRAT-R (reading), N-back, CPT "X" Task	-	BD < HC = BD-RL; WAIS-R (Vocabulary & Block Design)	-	2 BD-RLs had past MDD episodes
			-	BD-RL = HC: CPT "X" Task		
			-	BD-RL < HC: N-back RT		
			-	BD-RL = WRAT-R		
Antila et al. (2011)	32 BD-RL (UFDR) 40 BD 55 HC	WMS-R (DST-F, DST-B, VS-F, VS-B, CVLT, TMT-A, TMT-B, WAIS-R (Vocabulary and DSC)	-	BD-RL = HC: CVLT (list learning, immediate & delayed recall, & recognition); WMS (DST WMS (VS); TMT-A; TMT-B	-	BD-RL: 8 had a lifetime axis I diagnosis
					-	BD-RL relationship to BD patients not specified
					-	Measured effect of processing speed (DSC) on other cognitive tests: BD < BD-RL (Cued short recall, Free and Cued delayed recall)
Schulze et al. (2011)	42 BD-RL (UFDR) 44 BD 47 HC	HSCT, WAIS-R (DST-B), CANTAB (SWM, CANTAB ID/ED Shift), WASIIQ (Vocabulary, Matrix Reasoning)	-	BD-RL < HC: HSCT (category A and B errors & overall performance (SS)	-	HC: A prior history of other psychiatric disorders was not an exclusion factor
			-	BD-RL = HC: DST-B, SWM, or ID/ED Shift, WASI (Vocabulary, Matrix Reasoning)	-	Control, patient, and relative groups were balanced for age, gender, and parental social class

Study	Sample	Tests	Main results		Commentaries	
					-	BD-RL: (11 parents, 25 siblings, 6 offspring)- Not independent from Kravariti et al. (2009)
Brand et al. (2012)	20 BD-RL (UFDR) 20 HC	AGNG, WRAT-3	-	BD-RL < HC: WRAT-3	-	Results persisted even after controlling for subclinical depression and mania in BD-RL
			-	BD-RL > HC: AGNG (biased during Negative Condition, but not positive condition)	-	Some BD-RLs had had a history of substance abuse, but not present during testing
Christodoulou et al. (2012)	17 BD-RL (FDR) 23 HC	HSCT, COWA (phonemic), WAIS-R (FSIQ,Vocabulary)	-	BD-RL = HC: HSCT (except for Type B errors, FSIQ	-	The sample is not independent from various studies (see Christodoulou et al. (2012) for further details).
			-	BD-RL < HC: COWA	-	BD-RLs: no history of current or lifetime Axis I disorder
Daban et al. (2012)	580 BD-RL (UFDR) 53 BD 60 HC	WAIS-III (DSC & Vocabulary)	-	BD-RL = HC = nBD: premorbid IQ (WAIS-III: Vocabulary)	-	The sample is not independent from Szoke et al. (2006)
			-	BD < BD-RL < HC: DSC	-	BD & BD-RL > HC: Years of education
Kim et al. (2012)	13 BD-RL (UFDR) 28 BD 18 HC	Change Task (Go & Change), WASI IQ	-	BD-RL = BD = HC: Change Task (Go & Change, WASI IQ)	-	Age Range: 17 years old.
					-	BD-RLs had no psychopathology and medication
Deveci et al. (2013)	30 BD-RL (high risk offspring) 37 HC	Kent E-G-Y Test (IQ), Porteus Maze Test (IQ), RAVLT, Memory Test, COWAT (phonemic), WISC-III: DST, TMT-A, TMT-B, ACTT, WCST (categories), SCWT, TOVA	-	BD = BD-RL = HC: E-G-Y Test (IQ)	-	BD-RL participants aged > 11 yrs < HC: RAVLT (total learning 1–5, delayed recall, recognition); ACTT; COWAT; DST (forward); TMT-A; TOVA (response time)
			-	BD-RL < HC: RAVLT (total learning 1–5, immediate & delayed recall, recognition); ACTT; TMT-A;		
			-	BD-RL = HC: WCST (categories), SCWT, TMT-B		
Drysdale et al. (2013)	7 BD-RL (UFDR) 36 BD 33 HC	NART, CVLT, VFT (semantic & phonemic processing), HSCT,	-	BD-RL = BD = HC: IQ, BSAT	-	BD-RLs were high risk relatives belonging to a single extended

Study	Sample	Tests	Main results	Commentaries
		BSAT	- BD-RL < HC($p < 0.05$): CVLT (free immediate recall), VFT (semantic)	family showing linkage of BD to a locus on chromosome 4. - BD-RL: No history of psychiatric diagnosis
Adleman et al. (2014)	15 BD-RL 34 HC	Flanker Task (ISV-RT), WASI	- BD-RL > HC: ISV-RT on all trials - BD-RL = HC: IQ(WASI)	- Participants were siblings and offspring ages 3.5–6.5 years old.
Civil Arslan et al. (2014)	55 BD-RL 30 BD 32 HC	SCWT, WCST (categories & perseverative errors), RAVLT, TMT-A, TMT-B	- BD-RL < HC; RAVLT (1–5 learning) - BD-RL < HC; RAVLT (recognition) - BD-RL = HC: RAVLT (delayed and immediate recall), TMT-A, SCWT (interference), TMT-B - BD-RL > HC;WCST (perseverative & categories)	- UFDR < BD & HC: Education Level
Brotman et al. (2014)	15 BD-RL (UFDR) 20 BD 29 HC	Parametric Faces Paradigm, WASI	- BDs & BD-RLs < HC: Parametric Faces Paradigm (rated face as less hostile). - BD-RL = BD = HC: IQ (WASI)	- BD-RL (60% had parent with BD; 33% sibling with BD; 6.7% both) - BD-RL with history of ADHD or anxiety disorders included - Age Range: 8–19 years old
Erol et al. (2014)	50 BD-RL (UFDR) 25 BD 75 HC	VFT (semantic), TMT-A,TMT -B, WCST (categories, perseverative), SCWT	- BD-RL < HC (matched only, $n = 50$): TMT-A, TMT-B, SCWT, but not VFT & WCST	- BD-RL were parents of BD patients - Assessment conducted in Turkey - HC matched to BD and BD-RL
Fears et al. (2014)	557 BD-RL 181 BD	CVLT, PFMT (delayed), WMS (LMT & VR), AIM, WASI (vocabulary & matrix reasoning), PCET, SST, SCWIT, TONI, IP-CPT, SCAP, DST-F, DST-B, T, DSC, TMT, D-KEFS	- Associated with BD: SST (Go), PFMT (delayed), SCAP, IP-CPT - Significantly heritable and associated with BD: SCWIT, LNST, DSC, TMT, CVLT	- Recruited nuclear family members, at least 2 offspring of BD and non BD parents. - Extensive pedigrees were phenotyped (mean, 29

Study	Sample	Tests	Main results		Commentaries	
		(letter and category fluency)		(delayed, total trials), WMS (LMT: delayed, immediate, recognition), D-KEFS (category)	-	individuals per family) BD were exclusively BDI
			-	Not associated with BD: AIM (abstraction & plus memory), MR, PCET, SST (stop), TONI, WASI (vocab), DST-B, DST-F, CVLT (intrusions, recognition, repetitions), WMS (VR), D-KEFS (letter), WASI(Matrix Reasoning)		
Reynolds et al. (2014)	20 BD-RL 20 HC	Happé Stories task, Picture Sequencing task, Eyes task	-	BD-RL < HC: Happé Social & Physical story conditions	-	Used CPT & Colour-Word Stroop Test-Inhibition condition to covary out attention & executive functioning

BD-RL: Relative of patient with bipolar disorder. UFDR: Unaffected first-degree relative of patient with bipolar disorder. BD: Patient with bipolar disorder. HC: Healthy control. EEMT: Emotional Expression Multimorph Task. WASI: Wechsler Abbreviated Scale of Intelligence. IQ: Intelligence Quotient. ADHD: Attention Deficit Hyperactive Disorder. DANVA: Diagnostic Analysis of Nonverbal Accuracy Scale. DAS: Differential Ability Scales. FCPF: Flanker Continuous Performance Test. FSIQ: Full Scale Intelligence Quotient. ISV-RT: Intrasubject Variability in Response Time. WAIS-R/III: Wechsler Adult Intelligence Scale. WMS/WMS-R: Wechsler Memory Scale-Revised. LMT: Logical Memory Test. VR: Visual Reproduction Task. PAL: Paired Associates Learning. DSC: Digit Symbol Coding. DST/DST-F/DST-B: Digit Span Test-Forward/Backward. VS/VS-F/VS-B: Visual Span/Forward/Backward. CVLT: California Verbal Learning Test. TMT-A/TMT-B: Trail Making Test- Part A/Part B. WISC-III: Wechsler Intelligence Scale For Children. SCWIT/SCWT: Stroop Color Word Interference Test. WCST: Wisconsin Card Sorting Test. ROCF/ROCFT/RCFT: Rey Osterrieth Complex Figure Test. Seidman WM INT: Seidman Working Memory/Interference Control Factor. CPT: Continuous Performance Test. VFT: Verbal Fluency Test. TOL: Tower Of London. IGT: Iowa Gambling Task. VPA: Verbal Pair Associates. PCET: Penn Conditional Exclusion Test. IP-CPT: Identical Pair-Continuous Performance Test. ODRT: Object Delayed Response Task. LNST: Letter Number Span Test. SDRT: Spatial Delayed Response Task. PFMT: Penn Face Memory Test. D-KEFS: Delis Kaplan Executive Function System. USTDR: Unaffected Second-And Third-Degree Relatives. RAVLT: Rey's Auditory Verbal Learning Test. DS-CPT: Degraded Stimulus-Continuous Performance Test. WRAT-3: Wide Range Achievement Test-Third Edition. AGNG: Affective Go/No-Go. FDR: First-Degree Relative. HSCT: Hayling Sentence Completion Test. COWA/T: Controlled Word Association Test. CANTAB: Cambridge Neuropsychological Test Automated Battery. SWM: Spatial Working Memory Task. CANTAB ID/ED: Cambridge Neuropsychological Test Automated Battery: Intradimensional/Extradimensional Shift.

ACTT: Auditory Consonant Trigram Test. TOVA: Test Of Variables of Attention. NART: National Adult Reading Test. BSAT: Brixton Spatial Anticipation Test. AIM: Abstraction, Inhibition, and Working Memory Task. SST: Stop Signal Task. TONI: Test of Nonverbal Intelligence. SCAP: Spatial Capacity Delayed Response Test.

Table 3

Differential deficit rates between bipolar patients and their relatives.

Domains	Neurocognitive Test	Bipolar Patients		% deficit	BD-RLs		% of deficit/quality endophenotype
		Deficit	No Deficit		Deficit	No Deficit	
Intelligence	Kent E-G-Y Test	-	-		-	1	-
	NART	-	2		-	1	C
	Porteus Maze Test	-	-		-	1	-
	WAIS Block Design	-	-		1	2	-
	WAIS Comprehension	1	-		1	-	A
	WAIS FSIQ	1	-		1	5	B
	WAIS Information	1	1		-	-	-
	WAIS Object Assembly	-	-		-	1	-
	WAIS Similarities	1	-		2	-	A
	WAIS Vocab	7	7		1	8	B
	WASI IQ	-	-		1	4	-
	WASI/Raven's Progressive Matrices	1	-		1	-	A
	WRAT	-	-		1	1	-
Total		**12**	**10**	**54%**	**9**	**24**	**B 27%**
Executive Functioning	AIM Abstraction	-	-		-	1	-
	BSAT	-	-		-	1	-
	Change Task	-	-		-	1	-
	D-KEFS Design Fluency	1	-		-	-	-
	HSCT	-	-		1	2	-
	CANTAB ID/ED Tasks	-	-		-	1	-
	Matrix Reasoning	-	-		-	2	-
	PCET	-	-		1	1	-
	SCWIT	14	3		4	3	A*
	SST (Go)	-	-		-	1	-
	SST (stop)	-	-		-	1	-
	TMT-B	15	2		3	4	B
	TONI	-	-		-	1	-
	Tower of Hanoi	3	-		-	-	-
	Tower of London	-	-		1	-	-
	Tower Test	1	-		-	-	-
	WCST-Categories	6	4		2	4	B
	WCST-Perseverative Errors	9	5		3	2	A*
Total		**49**	**14**	**78%**	**15**	**25**	**B 38%**
Attention	CPT	-	-		1	2	-
	CPT-II	1	-		-	-	-
	DS-CPT	3	-		-	1	B
	DST-B	6	-		1	1	A

Domains	Neurocognitive Test	Bipolar Patients		% deficit	BD-RLs		% of deficit/quality endophenotype
		Deficit	No Deficit		Deficit	No Deficit	
	DST-F	9	1		1	1	A
	Flanker CPT	-	-		1	-	-
	Flanker Task ISV-RT	-	-		1	-	-
	IGT	2	-		-	1	B
	IP-CPT	-	-		2	-	-
	N-Back Task	-	-		1	-	-
	TMT-A	16	-		3	4	B
	TOVA	-	-		1	-	-
	WMS-Mental Tracking	2	-		-	-	-
Total		**39**	**1**	**98%**	**12**	**10**	**A* 54%**
Processing Speed	WAIS III Digit Symbol Coding	5	-		5	1	A*
Total -		**5**	**-**	**100%**	**5**	**1**	**A* 83%**
Working Memory	AIM plus memory	-	-		-	1	-
	Corsi	-	-		1	-	-
	DST-B	6	1		1	5	B
	DST-F	2	1		2	4	B
	Information Subtest	1	1		-	-	-
	Letter Number Sequencing	2	1		2	-	A
	SCAP	-	-		1	-	-
	SDRT	-	-		1	-	-
	Seidman WM INT CPT	-	-		1	-	-
	SWM	-	-		-	1	-
	WISC-III/WAIS-III Arithmetic	-	-		1	-	-
	WM-MA 2 Back	1	-		-	-	-
Total -		**12**	**4**	**75%**	**10**	**11**	**B 48%**
Episodic Memory	Claeson-Dahl	-	1		-	-	-
	PFMT-Delayed	-	-		2	-	-
	PFMT-Immediate	-	-		1	-	-
	VPA Delayed	-	-		1	-	-
	VPA Immediate	-	-		1	-	-
Total		**-**	**1**	**0%**	**5**	**-**	**D 100%**
Verbal learning & Memory	CVLT- Delayed Recall	13	4		2	4	B
	CVLT- Immediate Recall	11	6		1	2	B
	CVLT- Total Trials	8	2		3	1	A
	CVLT-MISC	-	2		-	3	-
	CVLT-Recognition	5	3		-	4	B
	LMT- Delayed Recall	1	-		2	-	A
	LMT- Immediate Recall	1	-		2	-	A

Domains	Neurocognitive Test	Bipolar Patients		% deficit	BD-RLs		% of deficit/quality endophenotype
		Deficit	No Deficit		Deficit	No Deficit	
	LMT- MISC	4	-		-	-	-
	LMT- Recognition	-	-		1	-	-
	MBS- Serial Learning	1	1		-	-	-
	MBS-Delayed	3	-		-	-	-
	MBS-Free Delay Recall	-	1		-	-	-
	MBS-Immediate	2	-		-	-	-
	MBS-Recognition	-	2		-	-	-
	PAL	-	-		1	-	-
	RAVLT- Immediate Recall	-	-		1	1	-
	RAVLT- Total Learning	-	-		3	1	-
	RAVLT-Delayed Recall	-	-		2	1	-
	RAVLT-Recognition	-	-		1	-	-
Total -		**49**	**21**	**70%**	**19**	**17**	**A* 53%**
Visual-Spatial Learning & Memory	Bell's Test	1	-		-	-	-
	ODRT	-	-		1	-	-
	ROCFT	4	-		3	1	A*
	WMS- Visual Span Test	-	-		-	1	-
	WMS- VR Delayed	-	-		-	2	-
	WMS- VR Immediate	-	-		-	2	-
	WMS-R VSP Backward	-	-		1	2	-
	WMS-R VSP Forward	-	-		1	2	-
Total -		**5**	**-**	**100%**	**6**	**10**	**B 38%**
Verbal Fluency	COWA/T Animal Naming	11	1		-	-	-
	COWA/T FAS	7	4		2	-	A
	D-KEFS Category Fluency	2	-		2	-	A
	D-KEFS Category Switching	2	-		-	-	-
	D-KEFS Letter Fluency	2	-		1	1	A
	Phonological Fluency Test	2	1		-	-	-
	Semantic Fluency Test	-	1		-	-	-
	VFT- Semantic	-	-		2	1	A
	VFT: Phonemic	-	-		1	1	A
Total -		**26**	**7**	**81%**	**8**	**3**	**A* 73%**
Social Cognition & Emotion Processing	Affective Go/No Go Task	-	-		1	-	-
	DANVA	-	-		1	-	-
	EEMT	-	-		1	-	-
	Ekman-60	-	1		-	-	-
	Emotion Perception Test	-	2		-	-	-

Domains	Neurocognitive Test	Bipolar Patients		% deficit	BD-RLs		% of deficit/quality endophenotype
		Deficit	No Deficit		Deficit	No Deficit	
	Faux pas Test	1	1		-	-	-
	FEE	-	-		1	-	-
	FEPT	-	2		-	-	-
	Happé Stories Task	-	-		1	-	-
	PFP	-	-		1	-	-
	PGNGT	2	1		-	-	-
	Picture Sequencing Task	-	-		-	1	-
	REMT	-	1		-	-	-
	The Eyes Task	-	-		-	1	-
Total		**3**	**7**	**30%**	**6**	**2**	**D 75%**

A*: BD & BD-RLs < HC; Candidate Endophenotype

A: BD & BD-RLs < HC; “Trending” Candidate Endophenotype

B: BD < BD-RLs & HC; BD-RLs = HC

C: BD & BD-RL= HC

D: BD-RLs < BD & HC; BD = HC

IQ: Intelligence Quotient. NART: National Adult Reading Test. WAIS Vocab: Wechsler Adult Intelligence Scale (and variants) – Vocabulary subtest. WASI: Wechsler Abbreviated Scale of Intelligence. WRAT: Wide Range Achievement Test. AIM: Abstraction, Inhibition, and Working Memory Task. BSAT: Brixton Spatial Anticipation Test. CANTAB ID/ED: Cambridge Neuropsychological Test Automated Battery: Intradimensional/Extradimensional Shift. D-KEFS: Delis Kaplan Executive Function System. HSCT: Hayling Sentence Completion Test. PCET: Penn Conditional Exclusion Test. SCWIT: Stroop Color Word Interference Test (and variants). SST: Stop Signal Task. TMT-B: Trails Making Test-Part B. TONI: Test of Nonverbal Intelligence. WCST: Wisconsin Card Sorting Test. CPT: Continuous Performance Test. CPT-II: Continuous Performance Test-II. DS-CPT: Degraded Stimulus- Continuous Performance Test. DST/DST-F/DST-B: Digit Span Test-Forward/Backward. IP-CPT: Identical Pair-Continuous Performance Test. ISV-RT: Intrasubject Variability in Response Time. TOVA: Test Of Variables of Attention. WMS-R: Wechsler Memory Scale. LNST: Letter-Number Sequencing Test. SCAP: Spatial Capacity Delayed Response Test. SDRT: Spatial Delayed Response Task. Seidman WM INT: Seidman Working Memory/Interference Control Factor. SWM: Spatial Working Memory Task. WM-MA: Working Memory-Mental Arithmetic Test. PFMT: Penn Face Memory Test. VPA: Verbal Pair Associates. CVLT/-II: California Verbal Learning Test/-II. LMT: Logic Memory Test. MBS: Memory Battery of Signoret. PAL: Paired Associates Learning. RAVLT: Rey’s Auditory Verbal Learning Test. ROCF/T: Rey Osterrieth Complex Figure Test. ODRT: Object Delayed Response Task. WMS-VR: Wechsler Memory Scale-Visual Reproduction Task. COWA/T: Controlled Word Association Test. FAS: phonemic verbal fluency task from COWAT.VFT: Verbal Fluency Test. DANVA: Diagnostic Analysis of Nonverbal Accuracy Scale. EEMT: Emotional Expression Multimorph Task. FEE: Facial expressions of emotion: stimuli and tests. PFP: Parametric Faces Paradigm. PGNGT: Parametric Go/No-Go Task. RMET: Reading the Mind in the Eyes Test.

Table 4

Key findings from main studies on the association between BD patients and neurocognition.

Domain	Task	Subtest	Article[a]	Main findings	+/−
Executive Functioning	D-KEFS	Tower Test	(20)	BDI < HC in 3 of 5 conditions	+
	SCWIT	Not Specified	(9)	SCT (secs): BD HPS+ < HC; SCWT: BD HPS+ < HC	+
			(3)	SCT: BD-IN = BD-PI; BD-IN < HC; BD-PI = HC; SCWT: BD-PI = BD-IN = HC	+
			(18)	BD < HC	+
		D-KEFS	(20)	BDI < HC for 2/4 conditions (1nhibition/1nhibition & Set-Shifting)	+
			(16)	Interference: SABP < HP- & HC; HPS+ < HC; Set Shifting: SABP & HPS+ < HC.	+
		Interference	(21)	Working HC > working & non-working BDs	+
			(17)	BD = HC	−
			(5)	GTC BD = PTC BD < HC	+
			(10)	BD treated with Risperidone < HC	−
			(23)	BD < HC. No group × time interaction found.	+
			(19)	BD < HC	+
			(6)	BD > HC	+
			(1)	BDI < BDII < HC	+
			(15)	BD = HC	−
			(2)	LF BD & HF BD < HC	+
	TMT-B		(23)	BD < HC. No group × time interaction found.	+
			(19)	BD < HC	+
			(2)	BD LF < BD HF < HC	+
			(5)	PTC BD < GTC BD < HC	+
			(4)	BDII < HC. BDI = BDII; HC	+
			(13)	BDI < HC. BDI < BDII. BDII < HC	+
			(10)	BD treated with olanzapine < HC	−
			(15)	BD < HC	+
			(1)	BDI, BDII & HC Trending observed	−
			(18)	BD < HC	+
			(9)	BD < HC	+
			(17)	Subsyndromal and asymptomatic BD < HC	+
			(11)	Recurrent Ep. BD < 1st episode BD < & HC.	+
			(3)	BD-IN = BD-PI; BD-IN < HC;	+

Domain	Task	Subtest	Article[a]	Main findings	+/−
				BD-PI = HC	
			(22)	Hard criterion-cognitive-impaired patients < HC.	+
			(6)	BD > HC	+
			(21)	Working HC > working & non-working BD	+
	ToH		(19)	BD < HC	+
			(9)	BD < HC.	+
			(3)	BD-IN = BD-PI; BD-IN < HC; BD-PI = HC	+
	WCST	Total Errors	(14)	BDI = BII = HC	−
		Categories	(18)	BD < HC	+
			(17)	Subsyndromal and asymptomatic BD < HC.	+
			(5)	GTC BD = PTC BD = HC	−
			(23)	BD < HC. No group × time interaction found.	+
			(10)	BD treated with olanzapine, risperidone, & quetiapine = drug-naïve BD = HC	
			(2)	LF BD = HF BD = HC	−
			(11)	Recurrent Ep. BD < 1st episode BD & HC. 1st episode BD < HC.	+
			(19)	BD < HC	+
			(15)	BD < HC	+
			(1)	BDI = BDII = HC	−
		Perseverative Errors	(1)	BDI = BDII = HC	−
			(23)	BD < HC. No group × time interaction found.	+
			(19)	BD < HC	+
			(2)	LF BD = HF BD = HC	−
			(18)	BD < HC	+
			(21)	BD < HC	+
			(17)	Subsyndromal and asymptomatic BD < HC	+
			(5)	GTC BD = PTC BD < HC	+
			(22)	Hard criterion-cognitive-impaired patients < HC.	+
			(11)	Recurrent Ep. BD < 1st episode BD & HC. 1st episode BD < HC.	+
			(14)	BDI = BII = HC	−
			(10)	BD treated with olanzapine, risperidone, & quetiapine = drug-naïve BD = HC	
			(15)	BD = HC	−
			(6)	BD > HC	+

Domain	Task	Subtest	Article[a]	Main findings	+/−
Attention	WAIS-R/WAIS-III/ WAIS/WMS-R	DST-F	(14)	BDI < HC; BDI = BDII; BDII = HC	+
			(15)	BD < HC	+
			(5)	GTC BD = PTC BD. GTC BD < HC. PTC BD < HC	+
			(22)	Hard criterion-cognitive-impaired patients < HC	+
			(13)	BD I = BDII = HC.	−
			(9)	HPS− & HPS+ < HC	+
			(3)	BD-IN = BD-PI; BD-IN < HC; BD-PI < HC	+
			(10)	BD treated with olanzapine & risperidone < HC	+
			(1)	BDI & BDII < HC	+
			(2)	BD < HC; LF BD < HC; HF < HC; LF < HF	+
		DST-B	(2)	BD < HC; LF BD < HC; HF < HC; LF<HF	+
			(5)	GTC BD = PTC BD; GTC BD < HC; PTC BD < HC	+
			(9)	HPS− & HPS+ < HC	+
			(3)	BD-IN = BD-PI; BD-IN < HC; BD-PI < HC	+
			(15)	BD < HC	+
			(10)	BD treated with olanzapine < HC	+
	TMT-A	D-KEFS	(20)	BDI < HC in 3 of 4 conditions. BDII < HC in 2 of 4 conditions	+
			(2)	BD < HC; LF<HC; HF < HC	+
			(9)	BD HPS− & BD HPS + < HC	+
			(17)	Subsyndromal and asymptomatic BD < HC	+
			(5)	GTC BD = PT BD. GTC BD and PTC BD < HC	+
			(13)	BD I = BDII & HC. BDII < HC	+
			(14)	BDI < BDII < HC	+
			(23)	BD < HC. No group × time interaction found	+
			(10)	BD treated with olanzapine & risperidone < HC	+
			(1)	BDI & BDII < HC	+
			(18)	BD < HC	+
			(21)	Working HC > working & non-working BDs	+
			(19)	BD < HC	+
			(4)	BDI & BDII < HC	+
			(11)	Recurrent episode BD < 1st episode BD & HC. 1st episode BD < HC.	+

Domain	Task	Subtest	Article[a]	Main findings	+/−
			(3)	BD-IN = BD-PI; BD-IN < HC; BD-PI = HC	+
			(22)	Hard criterion-cognitive-impaired patients < HC	+
	CPT-II		(12)	BD < HC	+
	DS-CPT		(7)	BD had fewer *hits*, a longer *reaction time* and less *sensibility* than HC	+
			(6)	BD < HC (Not significant for Sensitivity A')	+
			(23)	Group effect for CPT hits. BD = HC; CPT sensitivity A'. No group × time interaction found.	+
	IGT		(8)	All BD groups chose risky decks significantly more often than HC	+
			(12)	BD < HC (except for first & second block)	+
	WMS	Mental Tracking	(9)	HPS−, HPS+ < HC	+
			(3)	BD-IN = BD-PI; BD-IN < HC; BD-PI = HC	+
Processing Speed	WAIS-III	DSC	(18)	BD < HC	+
			(21)	Working HC > working & non-working BD	+
			(16)	HPS− < HC;SA HPS+, BD HPS+ < HC.	+
			(17)	Subsyndromal and asymptomatic BD < HC	+
			(23)	BD < HC. No group × time interaction found.	+
Memory	Claeson-Dahl	Learning, Retention, Recognition	(20)	BDI = BDII = HC	−
	CVLT/ CVLT-II	Composite	(18)	BD < HC	−
		Not Specified	(16)	HPS+ BD = HPS−; HPS− BD = HC	−
		Total (Trials 1–5)	(6)	HC > BD	+
			(10)	BD treated with olanzapine & risperidole < HC. No group effect for drug-naive & quetiapine treated BD.	+
			(15)	BD = HC	−
			(2)	BD < HC. LF & HF BD < HC. LF BD < HF BD	+
			(21)	BD = HC	−
			(17)	Subsyndromal and asymptomatic BD < HC	+
			(16)	HPS+ < HC; HPS+ = HPS−; HPS− = HC.	+
			(5)	GTC BD > PTBD; GTC BD < HC; PTC BD < HC	+
			(23)	BD < HC. No group × time interaction found.	+

Domain	Task	Subtest	Article[a]	Main findings	+/−
			(1)	BDI < BDII < HC	+
		Short/immediate cued-recall	(10)	BD treated with olanzapine & risperidole < HC. No group effect for drug-naive & quetiapine treated BD.	+
			(5)	GTC BD = PTC BD. GTC BD < HC; PTC BD < HC	+
			(2)	BD < HC; LF BD < HC; HF < HC	+
			(6)	BD < HC	−
			(1)	BDI < BDII < HC	+
			(15)	BD = HC	−
			(21)	BD = HC	−
			(17)	Subsyndromal and asymptomatic BD < HC.	+
		Long/delayed cued-recall	(10)	BD treated with olanzapine & risperidole < HC. No group effect for drug-naive & quetiapine treated BD.	+
			(2)	BD < HC; LF BD < HC; HF < HC; LF < HF	+
			(15)	BD = HC	−
			(21)	BD = HC	−
			(17)	Subsyndromal and asymptomatic BD < HC	+
			(5)	GTC BD = PTC BD. GTC BD < HC. PTBD < HC	+
			(6)	BD < HC	+
			(1)	BDI < BDII < HC	+
		Short/immediate free-recall	(23)	BD < HC. No group × time interaction found.	+
			(10)	BD treated with olanzapine & risperidole < HC. No group effect for drug-naive & quetiapine treated BD.	+
			(15)	BD = HC	−
			(2)	BD < HC; LF BD < HC; HF < HC; LF < HF	+
			(21)	BD = HC	−
			(17)	Subsyndromal and asymptomatic BD < HC	+
			(5)	GTC BD = PTC BD. GTC BD < HC. PTC BD < HC	+
			(6)	BD < HC	−
			(1)	BDI < BDII < HC	+
		Long/Delayed free-recall	(23)	BD < HC. Group × time interaction found	+
			(10)	BD treated with olanzapine & risperidole < HC. No group effect for drug-naive & quetiapine treated BD.	+
			(15)	BD = HC	−

Domain	Task	Subtest	Article[a]	Main findings	+/−
			(21)	BD = HC	−
			(17)	Subsyndromal and asymptomatic BD < HC	+
			(5)	GTC BD = PTC BD; GTC BD < HC; PTC BD < HC	+
			(2)	BD < HC; LF BD < HC; HF < HC; LF < HF	+
			(6)	BD < HC	+
			(1)	BDI < BDII < HC	+
		Recognition	(1)	BDI < BDII < HC	+
			(23)	BD = HC; No group × time interaction found.	−
			(10)	BD treated with olanzapine & risperidole < HC. No group effect for drug-naive & quetiapine treated BD.	+
			(2)	BD < HC; LF BD < HC; HF < HC; LF < HF	+
			(15)	BD = HC	−
			(21)	BD = HC	−
			(5)	GTC BD = PTC BD. GTC BD < HC. PTC BD < HC	+
			(6)	BD < HC	+
	MBS	Immediate recall	(13)	BDI < HC; BDII < HC; BDI = BDII	+
			(14)	BDI = BDII < HC	+
		Delayed recall	(14)	BDI = BDII < HC	+
			(13)	BDI < HC; BDII < HC; BDI = BDII	+
			(22)	Hard criterion-cognitive-impaired patients < HC	+
		Serial Learning	(22)	Hard criterion-cognitive-impaired patients < HC	+
			(14)	BDI = BDII = HC	−
		Free delay recall	(14)	BDI = BDII = HC	−
		Recognition	(14)	BDI = BDII = HC	−
			(22)	Hard criterion-cognitive-impaired = Hard criterion-cognitive-preserved = HC	
	WAIS-R	Information Subtest	(9)	BD < HC	+
			(3)	HPS− = HPS+ = HC	−
	WAIS-R/ WAIS-III/ WAIS/WMS-R	DST-F	(11)	1st episode BD & Recurrent Episode BD < HC (WMS-R)	+
			(19)	BDI = BD II; BDII < HC; BDI < HC	+
		DST-B	(16)	SA & HPS+ < HC	+
			(11)	1st episode BD & Recurrent Episode BD < HC (WMS-R)	+
			(23)	BD = HC; No group × time interaction found.	−
			(19)	BD < HC	+

Domain	Task	Subtest	Article[a]	Main findings	+/−
			(6)	BD < HC	+
			(22)	Hard criterion-cognitive-impaired patients < HC	+
			(1)	BDI & BDII < HC	+
	WAIS-III	LNST	(4)	BDI & BDII < HC	+
			(17)	Asymptomatic BD = Symptomatic BD = HC	−
	WMS	LNST	(23)	BD < HC. No group × time interaction found.	+
	WM-MA	2-Back	(16)	SA & HPS+ < HC	+
	WMS-LMT	Learning & Recall	(16)	BD HPS+ & SA < HC & BD HPS−	+
		Unspecified	(9)	BD HPS− < HC; BD HPS+ < HC	+
			(3)	BD-IN = BD-PI; BD-IN < HC; BD-PI < HC	+
		Short Recall	(17)	Subsyndromal and asymptomatic BD < HC	+
		Delayed Recall	(17)	Subsyndromal and asymptomatic BD < HC	+
		All Subtests	(11)	Subsyndromal and asymptomatic BD < HC in all subtests except for visual reproduction.	+
	ROCF/ROCFT	Delay	(23)	BD < HC. No group × time interaction found.	+
			(21)	Working HC > working & non-working BD	+
		D-KEFS version	(20)	Overall large group differences in 3 of 5 conditions. Time to draw figure: BDI > HC; immediate recall: BDI < HC; recognition: BDI & BDII < HC)	+
			(6)	HC > BD	+
		Immediate Recall	(23)	BD < HC. No group × time interaction found.	+
			(21)	Working HC > working & non-working BD	+
			(6)	BD < HC	+
		Not Specified	(18)	BD < HC	+
	Bell's Test		(3)	BD-IN = BD-PI; BD-IN = HC; BD-PI < HC	+
Verbal Fluency	D-KEFS	Letter fluency (Phonemic)	(20)	BDI < HC	+
			(16)	HPS+ < HCs, but not worse than HPS−. HPS− = HC	+
		Category Fluency (semantic)	(16)	SABP < HPS− & HC; HPS+ < HC	+
			(20)	BDI, BDII < HC; BDI < HC; BDII < HC	+
		Category Switching (set shifting)	(16)	SABP & HPS+< HPS− & HC	+
			(20)	BDI, BDII < HC. BDI < HC; BDII < HC	+

Domain	Task	Subtest	Article[a]	Main findings	+/−
	Phonological Fluency Test		(22)	Hard criterion-cognitive-impaired patients < HC	+
			(13)	BD I = BDII = HC	−
			(14)	BDI & BDII < HC; BDI < BDII	+
	Semantic Fluency Test		(13)	BD I = BDII = HC	−
	COWAT/ COWA	Animal Naming Fluency (semantic fluency)	(3)	BD = HC	−
			(18)	BD < HC	+
			(21)	Working HC & nonworking HC > non-working BD	+
			(19)	BD < HC	+
			(17)	Subsyndromal and asymptomatic BD < HC	+
			(23)	BD < HC. No group × time interaction found.	+
			(5)	GTC BD = PT BD. GT BD < HC; PTC BD < HC	+
			(10)	BD treated with quetiapine, olanzapine & risperidone < HC	+
			(2)	BD < HC; LF BD < HC; HF < HC	+
			(6)	BD < HC	+
			(15)	BD < HC	+
			(1)	BDI & BDII < HC; BDI < HC; BDII < HC; BDI < BDII	+
		FAS (phonemic fluency)	(1)	BDI = BDII = HC	−
			(19)	BD < HC	+
			(15)	BD = HC	−
			(10)	BD treated with olanzapine & risperidone < HC	+
			(18)	BD < HC	+
			(17)	Subsyndromal & asymptomatic BD = HC	−
			(5)	GTC BD = PTC BD. GTC BD < HC; PTC BD < HC	+
			(23)	BD < HC. No group × time interaction found.	+
			(2)	LF = HF = HC	−
			(21)	Working HC > non-working BD	+
			(6)	BD < HC	+
Premorbid & Current IQ	WAIS-R/ WAIS/WAIS-III	Vocabulary Subtest	(6)	BD < HC	+
			(22)	Trending: hard criterion-cognitive-impaired patients < HC	−
			(14)	BD = HC	−
			(2)	HF & LF BD < HC	+
			(10)	BD < HC	+

Domain	Task	Subtest	Article[a]	Main findings	+/−
			(21)	BD = HC	−
			(1)	BD = HC	−
			(2)	GTC BD & PTC BD < HC	+
			(7)	HPS− = HPS+ < HC	+
			(11)	BD < HC	+
			(3)	BD = HC	−
			(18)	BD = HC	−
			(15)	BD = HC	−
			(19)	BD < HC	+
			(23)	BD < HC	+
			(17)	BD = HC	−
	WAIS-R	Information Subtest	(4)	BDI & BDII < HC	+
			(20)	BDI = BDII = HC	−
	WAIS-R	Comprehension & Similarities	(9)	BD HPS− < HC; BD HPS+ < HC.	+
			(3)	BD-IN = BD-PI; BD-IN < HC; BD-PI < HC	+
	WAIS-III	WMIIQ: Digits Forward, Backward, & LNST	(17)	Symptomatic BD = Asymptomatic BD = HC	−
	NART		(8)	Manic, Depressed, & Euthymic BD = HC	−
			(16)	HPS− = HPS+ = HC	−
	TRPM		(12)	BD = HC	−
	D-KEFS	Design Fluency	(20)	BDI & BDII < HC for Set Shifting condition only.	+
Social Cognition & Emotional Processing	Ekman-60		(13)	BD I = BDII = HC (except for fear, BDII < HC and BDI < HC)	
	EPT		(18)	BD SUD− = BD SUD+ = HC	−
			(21)	Working HC > non-working BD	−
	FEPT		(18)	BD = HC	−
			(21)	Working HC > non-working BD	−
	Faux pas Test	ToM Index & Memory Index	(13)	BD I = BDII < HC BD I = BDII = HC	+
	PGNGT		(18)	BD < HC	+
			(21)	Working HC > non-working BD	+
	RMET		(13)	BD I = BDII = HC	−
Motor Skills	SDMT		(9)	BD HPS− < BD HPS+ < HC	+
			(3)	BD-IN = BD-PI; BD-IN & BD-PI < HC	+
	PPT		(18)	BD < HC	+
			(21)	working & non-working BD < working HC	+

[a]Refer to Table 1 for information on Author and Year of Publication as indicated by the numbers in parenthesis.

Table 5

Meta-analysis findings on neuropsychological domains associated with bipolar disorder.

Article	Krabbendam, Arts, van Os, and Aleman (2005)	Robinson et al. (2006)	Torres, Boudreau, and Yatham (2007)	Arts et al. (2008)	Bora, Yucel, and Pantelis (2009)	Kurtz and Gerraty (2009)	Mann-Wrobel, Carreno, and Dickinson (2011)	Samame (2013)	Bourne et al. (2013)	Lee et al. (2014)
Aggregate Sample Size & Mean Age	762 BD	689 BD	948 BD (39.8)	679 BD 336 BD-RL	1446 (38.8) BD 443(38.5) BD-RL	1197 BD (38.91)	1026 BD (40.5)	650 BD	2876 BD (38.8)	341 BD (28.2)
Homogeneity Test	Heterogeneity observed	Heterogeneity observed	Homogenous	Heterogeneity observed	Heterogeneity observed	Heterogeneity observed	Heterogeneity observed	Heterogeneity observed	Heterogeneity observed	Heterogeneity observed
Psychomotor Speed		***			***	***				***
Attention		*** sustained attention	***	** sustained attention	*** sustained attention ⊙	**			**	*** ** attentional switching
Response Inhibition		***			*** ⊙				**	-
Executive Functioning	***	***	***	*** ⊙	*** ⊙	***	***		***	*** cognitive flexibility
Perceptual							**			
Abstraction and set shifting	** concept formation	***			** ⊙				**	
Verbal learning and memory	**	***	***	*** ⊙	*** ⊙	***			***	**
Memory	*** verbal working	** immediate		*** working		***	*** Episodic & working		** working Memory	
Visual Learning & memory	***			**	**					-
Visuo-perception				*		**			**	
Verbal fluency	***	**		***	**	**	***			**
Processing Speed			***		**		***		***	
Emotion Processing								**		
Decision Making								-		
Mentalizing skills	***							***		

BD: *** High ES; **Small ES; - No group differences seen. BD-RL: ⊙ Deficits found.