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Title: Convergent and Discriminant Neurocognitive Deficits in Adult Patients with Schizophrenia and Bipolar Disorder: A Systematic Review

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Keywords: neurocognitive deficits; schizophrenia; bipolar disorder

Abstract: Our aim is to systematically review extant studies directly comparing neurocognitive deficits in adults with either schizophrenia (SCZ) or bipolar disorder (BD), their clinical correlates, especially with regard to the level of shared findings in both conditions. Of the initially screened reports from January 2000 till December 2014, 36 studies satisfied the inclusion criteria, and were summarized into main findings. Similar deficits across neurocognitive domains were found in both conditions and there is evidence for comparable neurocognitive impairments across SCZ and BD. The effect size of neurocognitive deficits in patients with schizoaffective disorder, and BD with psychotic features occupy a position intermediate between SCZ and BD without psychotic features. Neurocognitive deficits correlated with socio-demographic (lower education), clinical (more hospitalizations, longer duration of illness, negative psychotic and depressive symptoms, non-remission status), treatment (anti-cholinergics, lithium administration) variables and lower psychosocial functioning. The convergent neurocognitive findings in both conditions support a continuum concept of psychotic disorders and further research is needed to clarify common and dissimilar progression of these neurocognitive deficits over time.

Highlights:

- Neurocognitive deficits are found in schizophrenia and bipolar disorder
- It is unclear how convergent are the neurocognitive deficits in both disorders
- This review found comparable neurocognitive deficits in both disorders
- Neurocognitive deficits are associated with clinical and treatment factors
- Evidence supports a continuum model of psychotic spectrum conditions

Running title: Neurocognitive Deficits in Schizophrenia and Bipolar Disorder

Title: Convergent and Discriminant Neurocognitive Deficits in Adult Patients with Schizophrenia and Bipolar Disorder: A Systematic Review

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Abstract

Our aim is to systematically review extant studies directly comparing neurocognitive deficits in adults with either schizophrenia (SCZ) or bipolar disorder (BD), their clinical correlates, especially with regard to the level of shared findings in both conditions. Of the initially screened reports from January 2000 till December 2014, 36 studies satisfied the inclusion criteria, and were summarized into main findings. Similar deficits across neurocognitive domains were found in both conditions and there is evidence for comparable neurocognitive impairments across SCZ and BD. The effect size of neurocognitive deficits in patients with schizoaffective disorder, and BD with psychotic features occupy a position intermediate between SCZ and BD without psychotic features. Neurocognitive deficits correlated with socio-demographic (lower education), clinical (more hospitalizations, longer duration of illness, negative psychotic and depressive symptoms, non-remission status), treatment (anti-cholinergics, lithium administration) variables and lower psychosocial functioning. The convergent neurocognitive findings in both conditions support a continuum concept of psychotic disorders and further research is needed to clarify common and dissimilar progression of these neurocognitive deficits over time.

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1. Introduction

The Kraepelinian dichotomy, a prominent paradigm in psychiatry, has influenced the taxonomy for psychiatric disorders such as schizophrenia (SCZ) and bipolar disorder (BD) for many decades. The paradigm posits that patients with dementia praecox (schizophrenia) and manic depression (bipolar disorder) present as two separate psychotic disorders (Berrios & Beer, 1994; Kraepelin, 1913). Within this dichotomous framework, whilst both disorders are characterized by abnormalities in mood, behaviors, and neurocognitive functioning, they are often categorized by the presence of mania and depression in BD, or of psychotic symptoms such as delusions and hallucinations in SCZ. Earlier studies have suggested that the neuroimaging abnormalities and neurocognitive deficits observed in both patients groups appear to be disorder-specific, thus supporting the dichotomy paradigm (Bellivier et al, 2013; Depp et al, 2007; Ellison-Wright and Bullmore, 2010; Krabbendam et al., 2005; Murray et al, 2004; Schretlen et al., 2007; Seidman et al., 2002; Yu et al, 2010). Apart from the extant empirical evidence, the dichotomy paradigm is appealing due to conceptual simplicity, clinical and diagnostic convenience, hence such categorical disorders have persisted in the International Classification of Diseases (ICD-10) and in the newly-published Diagnostic Statistical Manual of Mental Disorders (DSM-5) (Angst, 2013; Moller et al., 2008; Sorias, 2012; Tandon et al, 2013).

However, recent evidence has argued for more similarities than differences between these two disorders. First, genome wide association studies (GWAS) have identified common susceptibility genes between SCZ and BD such as ZNF804A, CACNA1C, NRGN and PBRM1 (Bellivier et al, 2013; Craddock & Owen, 2005; Craddock et al., 2006; Goes et al.,

2012; Lichenstein et al., 2009; International Schizophrenia Consortium, 2009; Williams et al., 2011; Lee et al., 2012). Structural brain abnormalities in gray and white matter brain regions in SCZ and BD were also found (Anderson et al, 2013; Arnone et al, 2009; De Peri et al, 2012; Ellison-Wright & Bullmore, 2010; Tamminga et al, 2014), particularly in the temporal and frontal regions (Anderson et al, 2013). In addition, heterogeneity in the brain structural and functional changes do not seem to be diagnosis specific (Arnone et al, 2009; Tamminga et al, 2014). Third, clinicians frequently encounter patients with schizoaffective disorder (SA) and BD patients with prominent psychotic symptoms who do not fulfill diagnostic criteria for either category. In addition, dopamine dysregulation has been implicated in both disorders and as such, antipsychotic medications are used for managing symptoms of both SCZ and BD. A recent study by Tamminga et al (2014) involving 933 patients with SCZ, SA and psychotic BD probands found that the rates of use of antipsychotic drugs, mood stabilizers and antidepressants were similar across all 3 groups.

In this regard, whilst neurocognitive deficits have been acknowledged to be an important clinical finding in SCZ and BD, whether there are specifically shared and discreet patterns of neurocognitive deficits between SCZ and BD is not entirely clear (Vieta & Philips, 2007). Previous studies have suggested that patients with SCZ had more widespread and severe neurocognitive deficits compared to patients with BD (Lewandowski et al, 2011b; Murray et al, 2004). However, recent findings have also reported that both disorders exhibit comparable degree of neurocognitive deficit effect size across multiple domains (Altshuler et al, 2004; Depp et al, 2007; Ivleva et al, 2012; Kuswanto et al, 2013; Sánchez-Morla et al., 2009; Schretlen et al., 2007). Of note, some neurocognitive studies have showed diminished

diagnostic boundary between SCZ and BD when patients with SA and psychotic BD were included in the analyses (Hill et al, 2013; Lewandowski et al, 2011a; McClellan et al, 2004; Reichenberg et al, 2009; Simonsen et al, 2009; Smith et al, 2009) and BD patients with history of psychosis appear to be more cognitively impaired than those without such history in some studies (Martinez-Aran et al, 2008).

Recent data thus have challenged the current categorical diagnostic system and urged for some rethinking of psychotic disorders such as BD and SCZ as lying along a continuum rather than adhering to the Kraepelinian notion of dichotomous disorders. In this review, we aim to systematically review extant empirical studies which directly compared neurocognitive deficits between both disorders (including verbal memory, working memory, motor speed, attention, speed of processing and executive functions), their clinical correlates, and evaluate the level of shared findings in both conditions.

2. Methods

2.1 Literature Search

Following guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Liberati et al, 2009), we searched the National Centre of Biotechnology Information (NCBI), Pubmed/Medline, Scieverse, Scidirect, and Web-of-Science digital databases for empirical studies comparing neurocognitive functioning between patients with SCZ and BD between January 2000 and December 2014. Keywords for the literature search included 'schizophrenia', 'bipolar disorder', 'schizoaffective disorder', 'psychosis or psychoses' and 'cognitive or neurocognitive or neuropsychology' and 'deficits or impairments or abnormalities'. We identified potentially useful reports that were then screened as abstracts for meeting inclusion criteria. Promising studies were reviewed as full reports, and their bibliographies were screened for additional references.

2.2 Inclusion/Exclusion criteria

A report was selected for inclusion if: [a] they involved neurocognitive assessments and direct empirical comparisons between subjects diagnosed with SCZ and BD by internationally standard criteria such as DSM or ICD; and [b] was written in English.

2.3 Data Extraction

For each individual study we extracted variables including the number and type of subjects, socio-demographic characteristics, neurocognitive domains tested, and salient findings including clinical correlates.

2.4 Data Synthesis

The preceding data were organized in digitalized spreadsheets and then summarized in tables to guide preparation of critical assessments included in this manuscript and for independent consideration by readers. We considered essential findings with respect to comparative characteristics of neurocognitive functioning in subjects diagnosed with SCZ and BD.

3. Results

3.1 Retrieved Studies

We identified 124 potential publications, and of the initially screened reports, we excluded 63 as either duplicates or not meeting inclusion criteria. The remaining 61 reports were reviewed in detail; 25 were excluded: mainly for including subjects with diagnoses that are not relevant in this review or for not including direct empirical assessments and comparisons of neurocognitive functioning between the diagnoses of interest (SCZ and BD). 36 reports remained for inclusion in the study. Figure 1 shows the PRISMA flow chart detailing the filtering process of potential studies. The features and main findings of the included studies that examined neurocognitive functioning in SCZ and BD patients are summarized in Table 1.

We categorized the main findings into three main categories; patients compared with HC, neurocognitive functioning with SCZ patients who performed worse than BD patients (SCZ < BD), and neurocognitive functioning with comparable functioning between SCZ and BD (SCZ ≈ BD) (Table 1 and 2). In total, there were 2,571 SCZ patients, 1,938 BD patients and 2,418 HC subjects. Amongst the studies, 14 evaluated BD patients with history of psychotic features (subject N = 741), and seven studies evaluated patients with SA (subject N = 295). There were a total of 6 studies that did not enroll healthy controls (HC) (Dickerson et al, 2001; Martínez-Arán et al, 2002; McClellan et al, 2004; Mojtabai et al, 2000; Reichenberg et al, 2009; Verdoux & Liraud, 2000). The scales or measures administered by these studies are summarized in Table 3.

3.2 Neurocognitive domains implicated in SCZ and BD

3.2.1 Verbal memory

Verbal memory is a complex process by which individuals learn, retain and retrieve specific verbal information (Jayakar et al, 2015). It is often evaluated with tests of recall and/or recognition of word lists or storylines. These largely include components from the Wechsler Memory Scale (WMS), California Verbal Learning Test (CVLT), Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), and the Verbal Memory section of the Brief Assessment of Cognition in Schizophrenia (BACS). There were 26 studies which assessed verbal memory in SCZ and BD patients. Overall, most of the studies reported poorer performance in verbal memory in SCZ and BD patients when compared to HC. There were equal numbers of reports for worse verbal memory function in SCZ patients compared to BD patients (16 studies) as well as comparable degree of verbal memory impairments between them (15 studies, Table 2). Patients with SCZ tended to perform worse during learning and acquisition of memory compared to BD patients, and yet displayed comparable degree of deficits during retention and recall. There was no study that reported worse verbal memory function in BD patients compared to SCZ patients.

3.2.2 Working memory

Working memory is a cognitive domain that involves maintenance of relevant information where it can be processed or manipulated for problem-solving or goal-guided behavior (Baddeley & Hitch, 1974). The majority of the studies employed digit span (forward and backward), digit sequencing, and letter-number sequencing tasks to assess working memory. Out of the 21 studies that assessed working memory, only four studies found no

significant main effect of diagnosis (Brissos et al, 2008; Martínez-Arán et al, 2002; McClellan et al, 2004; Varga et al, 2007). Studies which reported significant main effect of diagnosis reported worse working memory in patients groups compared to HC group. However, 16 of these studies reported no significant difference between patients groups after controlling for covariates of clinical and socio-demographic factors. Studies that found significant difference between patients groups reported significantly lower scores in SCZ compared to BD patients during working memory tasks ($p < .001$; Dickerson et al, 2004; Hill et al, 2013; Simonsen et al, 2011), though one study reported that this difference had a small effect size (Dickerson et al, 2001). Of note, SCZ patients generally performed worse compared to BD patients when performing digit span forward, yet BD and SCZ patients were similarly impaired when performing digit span backward (Ancín et al, 2013; Meesters et al, 2013; Zabala et al, 2010).

3.2.3 Motor speed

Motor speed, which requires dexterity as well as visual-motor control and coordination, has been shown to be an important indicator and predictor of cognitive and physical functionality (Austin et al, 2011). In the reviewed studies, motor speed was assessed by administering timed motor tasks such as Grooved Pegboard, BACS Motor Token Task, and Finger Tapping Test, with dominant and non-dominant hand. The HC group performed significantly better compared to BD and SCZ patients. Out of the 9 studies which investigated motor speed, only 3 studies reported significant difference between SCZ and BD patients whereby BD patients performed better than SCZ patients after controlling for IQ and other covariates (Cholet et al, 2014; Hill et al, 2013; Schretlen et al, 2007).

3.2.4 Verbal fluency

Verbal fluency is defined as the ability to form and express words in accordance with required criteria (Wysokiński et al, 2010). In the studies examined, verbal fluency was operationalized as the number of words generated in a restricted category within a given amount of time (e.g. 60 seconds). Verbal fluency tasks are often divided into two categories: letter and semantic fluency. Letter fluency involved naming objects or verbs that start with a particular letter (e.g. F, A and S), whilst semantic fluency required subjects to name words that are congruent to a specific category (e.g. animals, supermarket items). There were 22 studies which measured verbal fluency performance. Five studies did not find significant group effect (Altshuler et al, 2004; Brissos et al, 2008; Kuswanto et al, 2013; Martínez-Arán et al, 2002; McClellan et al, 2004). From studies which found significant diagnosis effect, 15 studies reported no significant difference between SCZ and BD groups after controlling for covariates such as age, gender and IQ. Four studies showed that different results could be contributed by the type of verbal fluency tasks used (Ancín et al, 2013; Meesters et al, 2013; Rossell, 2006; Schretlen et al, 2007)

3.2.5 Attention & speed of processing

Attention is the ability to maintain selective, sustained focus on an activity (Papadopoulos et al, 2014). Speed of processing is typically defined as the ability to fluently complete simple, repetitive tasks (Schneider & McGrew, 2012). The two are related, as processing speed often requires attention and focused concentration on the task at hand. We reviewed 22 studies which employed various types of symbol coding or digit symbol tasks, Trail-Making-Test A (TMT A) and Continuous Performance Test (CPT) to assess these

neurocognitive domains. The majority of the studies found significant impairments within patients with SCZ and BD in comparison to HC. When BD and SCZ patients were directly compared, there were comparable numbers of studies within which SCZ patients performed significantly poorer than BD patients regardless of the neurocognitive tests used.

3.2.6 Executive function

Executive function is an umbrella term for a set of abilities including but are not limited to, planning and sequencing, problem-solving, abstract thinking, cognitive flexibility, and self-regulatory mechanisms such as inhibitory control (Burgess et al, 2000; Damasio, 1995; Grafman & Litvan, 1999; Shallice, 1988; Stuss & Benson, 1986). In this review, we examined 27 studies employing various executive tasks such as WCST, Tower of London or Tower of Hanoi, Stroop test and Trail-Making-Test B (TMT B). A number of studies employing the WCST measured both the percentage of choosing the category correctly and the number of preservative errors made by the subjects. Overall, the HC group performed significantly better compared to SCZ and BD patients, except in two studies in which diagnosis effect was not significant (Frangou et al, 2006; Verdoux & Liraud, 2000). The HC group scored higher in picking correct categories in comparison to BD and SCZ patients, but direct comparisons between SCZ and BD were more inconsistent in that five studies reported better performance in BD patients compared with SCZ patients (Altshuler et al, 2004; Martínez-Arán et al, 2002; Rossi et al, 2000; Schretlen et al, 2007; Seidman et al, 2002) but others reported no difference between patients groups (Ancín et al, 2013; Arduini et al, 2003; Depp et al, 2007; McClellan et al, 2004; Sánchez-Morla et al, 2009; Smith et al, 2009; Varga et al, 2007; Zabala et al, 2010). In terms of percentage of preservative errors, the majority of

the studies found no significant difference between the patients groups. Similarly, studies involving TMT B, Stroop tests and BACS Tower of London found conflicting results. In one study, patients with schizoaffective disorder performed significantly better than SCZ patients but worse than BD patients (Hill et al, 2013); yet another study found a comparable degree of deficits between SCZ, schizoaffective disorder and BD patients with psychotic features (Smith et al, 2009).

3.3 Clinical correlates of neurocognitive impairments in SCZ and BD

Regarding age, the majority of the neurocognitive studies matched age amongst their subjects groups. This was crucial because older age was associated with lower scores on neuropsychiatric assessments (Barrett et al, 2009; Kuswanto et al, 2013; Lewandowski et al, 2011; Mojtabai et al, 2000; Simonsen et al, 2011; Szoke et al, 2013). However, several studies found that neurocognitive studies which included older psychotic patients above 50 years old did not find age to be significant in moderating variable performance (Cholet et al, 2014; Depp et al, 2007; Meesters et al, 2013). Gender was also commonly matched amongst the subject groups, but its effect on neurocognitive performance was less commonly studied. Only two studies reported significant gender and diagnosis interactions in which female patients performing significantly better than their male counterparts in WAIS-III subscales, CVLT-II scale, and D-KEFS Verbal Fluency (Simonsen et al, 2011), as well as in the majority of RBANS subscales, except for RBANS List Learning and Story Memory Task (Gogos et al, 2010).

Healthy controls were reported to have significantly more years of education compared to BD and SCZ, and when education was not matched between patients groups, BD patients tended to have significantly more years of education compared to SCZ patients (Altshuler et al, 2004; Ancín et al 2013; Dickerson et al, 2004; Kuswanto et al, 2013; Lee et al, 2013; Meesters et al, 2013; Seidman et al, 2002; Simonsen et al, 2011). Years of education were found to be positively correlated with various neurocognitive scores such as BACS verbal memory, verbal fluency, digit sequencing and symbol coding tasks (Cholet et al, 2014), RBANS total scores (Dickerson et al 2004), D-KEF verbal fluency, TMT A/B, WCST and SWCT (Lewandowski et al, 2011; Szoke et al, 2008), and WAIS-R and WAIS-III Digit Span and Digit Symbol (Depp et al, 2007; Simonsen et al, 2011).

The majority of studies controlled for clinical factors such as age of onset, illness duration, and the number of hospitalizations. When correlational analyses were performed with neurocognitive performance, several studies found no correlations between these clinical factors and the neurocognitive measures (Althsuler et al, 2004; Depp et al, 2007; Krabbendam et al, 2000; Kuswanto et al, 2013; Lee et al, 2013; Lewandowski et al, 2011; Reichenberg et al, 2009; Rossi et al, 2000; Verdoux & Liraud, 2000). Significant variables in other studies included the number of hospitalization, duration of illness as well as the number of mania and psychotic episodes which were positively correlated with the severity of neurocognitive deficits using various measures (Ancín et al, 2013; Sánchez-Morla, 2009; Simonsen et al, 2011). Regarding BACS, longer illness duration, greater number of hospitalizations and early onset of BD were also negatively correlated with BACS Total, Token Motor Task and Tower of London scores (Cholet et al, 2014).

Symptom presentation appeared to affect cognitive performance in some studies. Most studies have shown that negative symptoms are more commonly associated with greater impairments across most neurocognitive domains compared with positive psychotic symptoms (Ancín et al, 2013; Dickerson et al, 2004; Simonsen et al, 2011; Smith et al, 2009; Zanelli et al, 2010). In a study by Barrett et al (2009), group differences in verbal fluency reached trend levels after controlling for depression, but were no longer significant when negative symptoms were controlled for. The number of depressive episodes was also correlated with poorer scores in tests of WAIS-R Digit Span Backward, semantic and letter fluency tasks in BD patients (Ancín et al, 2013). However, other findings have challenged this view. Simonesen et al (2011) found that the number of manic episodes was inversely correlated with performance on verbal memory, verbal fluency and working memory tasks compared to depressive episodes. In addition, higher total PANSS scores were associated with poorer attention in patients with SCZ (Zabala et al, 2010).

Regarding history of psychotic features, ten studies recruited patients with BD and history or concurrent psychotic features at the time of the study (Depp et al, 2007; Frangou et al, 2006; Hill et al, 2013; Kuswanto et al, 2013; Lee et al, 2013; Lewandowski et al, 2011; Mojtabai et al, 2000; Simonsen et al, 2011; Smith et al, 2009; Szoke et al, 2008; Verdoux & Liraud, 2000). When patients with schizoaffective disorder (SA) and BD with psychotic features were compared alongside patients with SCZ and HC, a pattern of decline across all neurocognitive domains was observed, from BD with psychotic features, to SA, and the greatest level of deficit being observed in SCZ (Hill et al, 2013). This suggests there are overlapping

neurocognitive deficits in psychosis across SCZ spectrum disorders and BD. However, results are mixed. Other studies reported similar degree of neurocognitive deficits between BD patients with and without psychotic features, suggesting that psychotic features may not specifically influence cognitive performance within BD (Ancín et al 2013; Glahn et al, 2006; Krabbendam et al, 2000; Kuswanto et al, 2013; Lee et al, 2013; Sánchez-Morla, 2009; Szoke et al, 2008), but this might be influenced by power issues. Some studies indicate that a history of psychosis may be a risk factor for cognitive impairment (Martinez-Aran et al, 2008) and studies comparing cognitive performance in bipolar I and bipolar II disorder (Torrent et al, 2006; Simonsen et al, 2011; Solé et al 2011, 2012) suggest that cognitive impairment may correlate with illness severity; this would explain the greatest impairment being associated with a high number of manic episodes (which are more likely to go along with psychotic symptoms than other episode types) and would again introduce some dimensionality to the potential differences between schizophrenia and bipolar disorder as far as cognition is concerned (López-Jaramillo et al, 2010; Bonnín et al, 2014; Martínez-Arán & Vieta, 2015).

In terms of medications, the findings were inconsistent regarding the effect of medications on neurocognitive impairments in SCZ and BD. The total number of psychotropic drugs used was inversely correlated with TMT-A/B and verbal fluency performance for both BD and SCZ groups, and with Digit Span and Stroop Test scores in SCZ patients (Ancín et al 2013). The use of antipsychotic medications was significantly associated with poorer performance on WCST (Altshuler et al, 2004) and Global Cognitive Functioning (Depp et al, 2007) compared with those not using antipsychotics. Anticholinergic medication in SCZ was associated with poorer verbal memory in SCZ (Altshuler et al, 2004). Likewise, patients

taking lithium had worse cognitive functions than those not taking lithium (Depp et al, 2007), although other studies have found no difference (Altshuler et al, 2004). Yet other studies have also found little effect of medications on neurocognitive performance in BD or SCZ patients (Hill et al, 2013; Kuswanto et al, 2013; Reichenberg et al, 2009; Seidman et al, 2002; Zabala et al, 2010). Careful interpretations of these results are warranted, as the sample sizes tend to be too small when they were sub-divided based on medication groups. History of alcohol and/or substance abuse/dependence was reported to have minimal effect on neurocognitive scores (Altshuler et al, 2004; Depp et al, 2007; Hill et al, 2013), but current substance use can be detrimental (van Gorp et al, 1998; Sánchez-Moreno et al, 2009).

The clinical state such as remission status of the patients during the time of testing was also considered in some of the neurocognitive studies. For example, a study conducted by Meesters et al (2013) separately analyzed SCZ patients in symptomatic remission (n = 20) with those not in symptomatic remission (n = 47). Non-remitted SCZ patients were found to have significantly worse scores compared to BD patients, but remitted SCZ patients were equally impaired as BD patients in all neurocognitive tests. Similarly when BD subtypes were also compared, BD type I and type II disorders were equally impaired in all neurocognitive domains (Krabbendam et al, 2000; Lee et al, 2013)

There were two studies which specifically examined the association between insight and neurocognitive deficits in BD and SCZ using the Scale to assess the Unawareness of Mental Disorder (SUMD). Arduini et al (2003) reported no significant difference in insight between SCZ and BD, nor was there significant correlations between insight, SANS & SAPS

scores and WCST scores. Varga et al (2007) also found similar levels of awareness of mental illness on SUMD between the two patient groups, but patients with SCZ scored significantly higher for SUMD awareness and misattribution subscales (indicating poorer insight) compared to BD patients. Furthermore, impaired insight was associated with various neuropsychological deficits including working memory, verbal learning, attention, set shifting/executive functions and motor function in both patients groups. Of note, Varga et al (2007) reported SCZ group to have significantly lower level of IQ and education as well as higher level of psychopathology compared to BD group, whereas in the other study SCZ and BD did not differ significantly on any demographic and clinical variables except for higher negative symptoms in SCZ compared to BD (Arduini et al, 2003).

Psychosocial functioning was often measured using Global Assessment of Functioning (GAF) scale in most reviewed studies. Patients with BD had higher scores in GAF scale compared to those with SCZ (Altshuler et al, 2004; Caletti et al, 2014; Kuswanto et al, 2013; Martínez-Arán et al, 2002; Simonsen et al, 2011; Varga et al, 2007). However, few studies investigated the relationship between GAF and neurocognitive performance but available studies found that lower GAF scores were associated with poorer neurocognitive functioning across most domains except for BACS Tower of London (Caletti et al, 2013; Cholet et al, 2014; Kuswanto et al, 2013; Martínez-Arán et al, 2002; Sánchez-Morla, 2009). On the other hand, only one study looked at the relationship between QOL and neurocognitive performances in BD and SCZ. BD and SCZ patients reported significantly lower scores on the physical, psychological and social domains of WHOQOL-BREF scale compared to HC, but there were no significant differences between the disorders (Brissos et al, 2008). Brissos et al

(2008) noted negative correlations between WHOQOL-BREF domains with various cognitive tasks such as TMT-A, TMT-B, ToH and SWCT in BD patients, but not in SCZ patients.

4. Discussion

There are several overarching key findings in this systematic review. First, extensive neurocognitive impairments were observed across domains in SCZ and BD and whilst some studies have found worse neurocognitive deficits in SCZ than BD, there is evidence for comparable neurocognitive impairments in BD and SCZ. Second, when other psychotic syndromes were included in the studies such as schizoaffective disorder and BD with psychotic features, there is an increasing level of neurocognitive impairment from BD patients to schizoaffective disorder/BD with psychotic features and SCZ. These findings support the continuum concept of psychosis rather than the Kraepelinian concept of dichotomous psychotic disorders at least when examined cross-sectionally. Third, poorer neurocognitive functioning correlated with clinical factors including socio-demographic (lower education), illness (more hospitalizations, longer duration of illness, negative psychotic and depressive symptoms, non-remission status), treatment (anticholinergics, lithium administration) variables and lower psychosocial functioning. These findings urge the rethinking of rigid categorical diagnostic system and suggest incorporating a more dimensional framework for psychotic spectrum conditions.

Whilst the extant studies point to evidence of comparable neurocognitive deficits across SZ and BD, the underlying genetic basis for shared neurocognitive deficits in BD and SCZ patients is likely to be complex. Common susceptibility genes such as catechol-O-methyltransferase (COMT) and brain-derived neurotrophic factor (BDNF) were found to be associated with verbal working memory, problem solving, attention and executive functioning (Kurnianingsih et al, 2011). Interestingly, recent genetic studies have reported that first-degree

relatives of patients with Attention Deficit and Hyperactivity Disorder (ADHD) were at increased risk of developing both BD and SCZ, suggesting a likely genetic relationship of attention deficits with psychotic disorders (Hamshere et al, 2013; Larsson et al, 2013).

On a brain structural level, studies have found substantial overlap with areas of gray matter reduction in both diseases, particularly in the prefrontal cortex, medial temporal lobe, thalamus and paralimbic regions such as anterior cingulate and insula, although extent of gray matter reductions in BD was less compared with patients with SCZ (Anderson et al, 2013; Ellison-Wright & Bullmore, 2010; Yu et al, 2010). Shared white matter endophenotypes could also be observed in terms of the reduction of white matter volume in the left frontal and temporoparietal regions (McDonald et al, 2004), as well as dysconnectivity in fronto-subcortical and fronto-temporo-parietal regions, which may have contributed to shared deficits in verbal memory, verbal fluency, attention, psychomotor speed (van Beilen et al, 2013) and executive functions (Bora et al, 2008). Furthermore, a systemic review on previous electrophysiological studies by Bora et al (2008) concluded similar trait and state-related electrophysiological disturbances underlying both conditions. It is also noteworthy to mention that a recent neuroimaging meta-analysis conducted by Goodkind et al (2015) identified a transdiagnostic pattern of gray matter loss in regions of the dorsal anterior cingulate and anterior insula across six different psychiatric disorders, including SCZ and BD. Moreover, this decrease in regional gray matter was found to be associated with poorer executive functioning and is not likely to be attributed to medication effects. Taken together, this may illustrate a general mapping between a broad range of cognitive functions and neural integrity across psychiatric illnesses.

Previous reports have found that deficits during the encoding stage largely account for the verbal memory impairments in SCZ (Chepenik et al, 2012; Cirillo & Seidman, 2003; Leavitt & Goldberg, 2009) and BD patients (McKenna et al, 2013; Raust et al, 2014). Medial temporal lobe structures such as the hippocampus is responsible for encoding new information into semantic categories (Cirillo & Seidman et al, 2003), and has been found to be smaller in patients with BD and SCZ which contributes to fronto-subcortical dysconnectivity affecting information retrieval and semantic processing (Chepenik et al, 2012; Stone & Hsi, 2011).

Of note, speed of processing impacts a number of higher order of neurocognitive processes in a bottom-up manner (Brébion et al, 2013), serving as an intermediate between verbal memory and verbal fluency (Ojeda et al, 2008, van Beilen et al, 2004). Speed of processing has been showed to be involved in memory efficiency which requires effortful process of semantic organization and encoding (Brébion et al, 2013; Ojeda et al, 2008). An intact storage of semantic information and an efficient access to the information is needed for verbal fluency tasks, which is primarily mediated by the fronto-temporal circuitry (van Beilen et al, 2004). Fronto-temporal dysconnectivity in both SCZ and BD may thus contribute to the impairments in both verbal fluency and verbal memory tasks (van Beilen et al, 2004).

Deficits in working memory and executive functioning have also been observed in SCZ and BD patients. The prefrontal cortical network, particularly in the dorsolateral prefrontal cortex (DLPFC), has been identified as the critical region for working memory dysfunction in SCZ and BD patients (Hamilton et al, 2009; Lett et al, 2014). In fact, both SCZ and BD

patients activated similar working memory network as HC subjects, involving the PFC, primary and supplementary motor cortex, visual cortex and DLFPC. Earlier studies found that HC subjects had greater activations of working memory network compared with patients with BD, and SCZ showed significantly less activations compared with BD and HC (Brandt et al, 2014; Hamilton et al, 2009). Furthermore, deficits in top-down attention disrupt effective inhibition of extraneous information during working memory (Lett et al, 2014). Executive functioning depends on an intact PFC and executive functioning deficits can be gleaned from poorer cognitive flexibility and high percentage of category and/or preservative errors during WCST, lack of inhibitory control during Stroop Tests, and poorer cognitive planning during Tower of London/Hanoi. As executive functioning also interacts with attention and working memory, executive functioning deficits in patients with psychotic disorders are related to circuitry abnormalities involving the prefronto-striato-thalamic, prefronto-parietal, and prefronto-temporal neural networks (Orellana & Slachevsky, 2013).

How do the clinical correlates inform the differentiation of neurocognitive impairments in SCZ and BD? There are common and different observed neuro-developmental processes observed for both SCZ and BD. For example, early neuroanatomical changes and neurocognitive impairments can be observed premorbidly proceeding to the onset of SCZ, which are absent in BD (Demjaha et al, 2012; Lewandowski et al, 2011b; Murray et al, 2004; Napal et al, 2012). A review by Napal et al (2012) observed that patients with early-onset SCZ tended to have greater deficits in attention, verbal fluency, global cognition, IQ and visuospatial skills compared to those with delayed onset SCZ. These early, neurodevelopmentally influenced cognitive deficits could reflect underlying neuroanatomical

aberrations such as more progressive cortical loss, particularly in the amygdala, hippocampus and lateral ventricles in SCZ (Arnone et al, 2009; Bellivier et al, 2013; Demjaha et al, 2012; Murray et al, 2004; Yu et al, 2010). In contrast, BD patients are thought to experience a more normal developmental stage prior to the onset of the illness. Deterioration in neurocognitive and social functioning in BD are observed later and positively associated with the duration of illness and the disease course (Lewandowski et al, 2011b; Napal et al, 2012). The subsequent affective episodes may affect and worsen neurocognitive functioning with each recurrence as supported by correlations of neurocognitive deficits with number of manic, depressive and psychotic episodes, hospitalizations and duration of illness (Martinez-Aran et al, 2004; López-Jaramillo et al, 2010; Rosa et al, 2014).

Patients with a history of psychosis, including patients with schizoaffective disorder or psychotic BD, were found with poorer neurocognitive functioning compared to those without psychotic features regardless of their clinical diagnoses (Bora et al, 2008; Hill et al, 2013;Simonsen et al, 2011). Further examination found that in studies which included patients with SA and BD with psychotic features (Ancín et al, 2013; Lewandowski et al, 2011a; Reichenberg et al, 2009; Simonsen et al, 2011; Tamminga et al, 2014), patients with SA and BD without psychotic features performed better in neurocognitive functioning compared with SCZ (Hill et al, 2013; Tamminga et al, 2014) and BD with psychotic features (Simonsen et al, 2011) respectively, highlighting a spectrum of neurocognitive deficits towards a continuum of psychosis. Overall, these findings also suggest that sample heterogeneity could potentially influence outcomes. .

We found that negative symptoms were significantly associated with neurocognitive dysfunctions in various neurocognitive domains (Ancín et al 2013; Dickerson et al, 2004; Simonsen et al, 2011; Smith et al, 2009; Zanelli et al, 2010). This is in line with previous findings which suggested that deficit syndrome of SCZ had more severe neurocognitive impairments in relation to non-deficit SCZ patients which are related to psychosocial outcomes (Dantas et al, 2011; Pegoraro et al, 2013; Polgár et al, 2010). As BD patients have less severe negative symptoms in comparison to SCZ and SA, this may partially explain the presence of greater neurocognitive impairment in SCZ and SA patients compared to BD patients. There is a lack of evidence for correlation between psychotic positive symptoms (despite their treatability with antipsychotic medications) and neurocognitive functioning in SCZ. This may be mediated by the observation that current antipsychotic medications which typically target and ameliorate positive symptoms such as hallucinations and delusions, often exert minimal or modest effect on neurocognitive deficits (Hill et al, 2013; Keefe et al, 2007; Kuswanto et al, 2013; Lett et al, 2014; Reichenberg et al, 2009; Seidman et al, 2002 Torrent et al, 2011). Anti-cholinergic medications can impair verbal memory in SCZ (Altshuler et al, 2004) but they do not account for other neurocognitive deficits (Cirillo & Seidman, 2003). Mood-stabilizers are, however, not free of cognitive side-effects (Mora et al, 2013; Muralidharan et al, 2015).

Older age has been associated with poorer neurocognitive functioning in patients (Barrett et al, 2009; Kuswanto et al, 2013; Simonsen et al, 2011), which is in line with that of other studies in which older age was associated with decreased gray matter volume (Schuster et al, 2012).

Variability in study samples also need to be taken into account. There seems to be a trend of smaller sample sizes of BD patients compared to SCZ patients and HC subjects. Smaller sizes for BD patients could potentially increase the risk of type II errors in some studies not finding significant differences between BD and SCZ; conversely, studies with small sample sizes with large effect sizes could have been attributed to Type I errors (Daban et al, 2006).

Given that this review clearly points to more similarities than differences between SCZ and BD in cross-sectional studies, a pertinent question is to what extent longitudinal studies support these findings. Again, most long-term studies indicate that the course and outcome of cognitive deficits is remarkably similar between SCZ and BD (Balanzá-Martínez et al, 2005; Tabarés-Seisdedos et al, 2008). However, the primary factor that appears to support qualitative differences in cognitive performance between SCZ and BD is the premorbid cognitive status of subjects who would later develop either condition (Vieta, 2014). Hence, several studies report a practical absence of premorbid cognitive deficits in BD, which differs in SCZ (Reichenberg et al, 2002; Cannon et al, 2002; Zammit et al, 2004; Tiihonen et al, 2005). This intriguing finding suggests that cognitive disturbance may be a final common pathway in both conditions, but that SCZ would better fit in a neurodevelopmental model of disease, whereas BD could be likened to neurodegenerative or neuroprogressive conditions (Goodwin et al, 2008). It is also possible that the BD population is actually composed of 2 groups, one with premorbid cognitive deficits and another one with supra-normal cognitive performance, thus giving the false impression of absence of deficits on average (Bora et al,

2015; Martino et al, 2015). Studies focusing on cognitive reserve may provide further hints to this hypothesis (Forcada et al, 2015).

4.1 Clinical implications and limitations

There are several clinical implications based on our findings. First, neurocognitive deficits have been found to be core deficits as well as predictive factors for psychosocial outcomes. Therefore, a better understanding on the neurocognitive deficits and its underlying biological basis may help better clinical management of our patients. For example, optimization of cognitive remediation therapy (CRT), together with pharmacological treatments, can be envisaged to target specific neurocognitive deficits in SCZ and BD (McGurk et al, 2007; Wykes et al, 2011). Interventions such as functional remediation may be able to assist in improving those functional outcomes that are heavily related to cognitive problems (Torrent et al, 2013). Second, whilst our findings have showed that impaired insight was associated with neurocognitive deficits in various domains for both illnesses (Arduini et al, 2003; Varga et al, 2007), recent studies have showed that the relationship between neurocognitive functions and insight is a bi-directional process in which neurocognitive deficits may contribute to poor insight and adherence to treatment in psychotic disorder and vice versa (Aleman et al, 2006; Lysaker et al, 2013). Third, it may be imperative to consider the contribution of neurocognitive functioning to nosology of psychotic spectrum conditions. In spite of the ongoing debate pertaining to the definitions and the boundaries between nosological entities in psychotic disorders, a dichotomous paradigm is predominantly retained in the new DSM-5 for a number of reasons. First, the DSM-IV construct of SCZ has been found to have high reliability and fair validity (Tandon et al, 2009). Second, DSM SCZ has

very high diagnostic stability, with 80-90% of patients receiving an initial diagnosis of SCZ retaining the diagnosis 1 – 10 years later (Bromet et al, 2011; Haahr et al, 2008; Tandon et al, 2013). In addition, there are a number of issues regarding the adoption of dimensional criteria into real practice due to impreciseness, hence not as well adopted (Maj, 2013; Barch et al 2013). As yet, while the inclusion of cognitive deficits as a characteristic symptom of SCZ was carefully considered, no changes were made because cognitive deficits have not been found to be sufficient in distinguishing SCZ with other 'boundary' disorders (Tandon et al, 2013). However, neurocognitive functioning is included as one of the eight domains for dimensional assessments of psychotic conditions in DSM 5, namely, psychotic symptoms (e.g. hallucinations, delusions, disorganized speech, abnormal psychomotor behavior and negative symptoms), cognitive impairment, depression and mania (APA 2013).

There are several limitations. First, our inclusion criteria required neurocognitive tasks to be administered in English and consequently restricted the number of studies included. Furthermore, some studies did not specify the language medium during administration of psychometric tests. We attempted to overcome this limitation by including studies in which neurocognitive measures did not require verbal tasks such as WCST, TMT A/B and psychomotor tests. Since many neurocognitive tasks require adequate language abilities, it would be interesting to investigate whether specific characteristics of language may potentially impact neurocognitive functions cross-culturally. Secondly, studies directly comparing longitudinal outcomes of neurocognitive impairments in SCZ and BD are sparse and future research would shed light on progressively similar or dissimilar trajectories of these neurocognitive deficits across different psychotic disorders.

In conclusion, we reviewed studies investigating neurocognitive deficits in SCZ and BD and found evidence to suggest comparable impairment across most cognitive domains in both conditions. Findings indicating that the degree of neurocognitive impairment in patients with schizoaffective disorder and BD with psychotic features lie between SCZ and BD without psychotic features support a spectrum an continuum model of psychotic conditions. Poorer neurocognitive functioning is also associated with socio-demographic, illness, treatment variables and lower psychosocial functioning which suggest areas for greater clinical attention and better optimization of management for these conditions. Further research is needed to clarify common and dissimilar progression of these neurocognitive deficits over time, their neurobiological underpinnings, as well the response of specific neurocognitive deficits to treatments for SCZ and BD.

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6. Abbreviations

ADHD – Attention deficit hyperactivity disorder

BACS – The Brief Assessment of Cognition in Schizophrenia

BD – Bipolar disorder

BDNF – Brain-derived neurotrophic factor

CACNA1C – Calcium Channel, Voltage-Dependent, L-Type, Alpha 1C Subunit

COMT – Catechol-O-methyl transferase

CPT – Continuous Performance Tasks

CVLT-II – California Verbal Learning Test - Second Edition

D-KEFS – Delis-Kaplan Executive Function System

DLPFC – Dorsolateral prefrontal cortex

DSM-5 – The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition

DSM-IV – The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition

GAF – Global Assessment of Functioning

GWAS – Genome wide association studies

HC – Healthy controls

ICD-10 – International Classification of Diseases and Related Health Problems 10th Revision

IQ – Intelligence quotient

NCBI – National Centre of Biotechnology Information

NRGN – Neurogranin (Protein Kinase C Substrate, RC3)

PFC – Prefrontal cortex

PBRM1 – Polybromo 1

RBANS – Repeatable Battery for the Assessment of Neuropsychological Status

SA – Schizoaffective disorder

SCZ – Schizophrenia

SWCT – Stroop Word-Color Test

TMT A – Trail Making Test A

TMT B – Trail Making Test B

ToH – Tower of Hanoi

WAIS-III – Wechsler Adult Intelligence Scale - Third Edition

WAIS-R – Wechsler Adult Intelligence Scale - Revised Edition

WCST – Wisconsin Card Sorting Test

WHOQOL-BREF – WHO Quality of Life-BREF

WMS – Wechsler Memory Scale

ZNF804A – Zinc finger protein 804A

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8. Figure Captions

Figure 1. PRISMA flowchart illustrating methodological steps in identifying empirical studies that were included in this systematic review.

Table 1
Click here to download Table(s): SCZBD_Review_Table1.docx

Table 1. Main findings of included studies comparing neurocognitive functioning between SCZ and BD

Authors	**Subjects**	**Age (SD), Sex (M/F)**	**Neurocognitive Task**	**Patients vs HC**	**SCZ < BD**	**SCZ ≈ BD**	**Clinical Correlates**
Altshuler et al (2004)	40 BD 20 SCZ 22 HC	49.9 (13.9) 50.0 (7.9) 51.8 (12.6) All male	CVLT VFT (FAS) TMT A/B WCST SCWT	SCZ < BD < HC: WCST (categories), TMT B SCZ, BD < HC: WCST (perseverative errors), CVLT SCZ < BD, HC: SWCT (color), TMT B SCZ < HC: SWCT (word), TMT A NS: VFT (FAS), SCWT (interference)	WCST (categories) TMT B	WCST (perseverative errors) CVLT VFT TMT A SWCT	<u>Clinical & demographic profiles</u>: Education years: SCZ < BD, HC GAF: SCZ < BD Gender, medication, marital status, age of onset & duration of illness: NS <u>Association with cognitive score</u>: BD with SCID diagnosis of prior alcohol dependence vs those without: NS Use of antipsychotic ↓ WCST categories, did not affect CVLT scores in BD Use of anticholinergics ↓ CVLT in SCZ SCZ taking typical vs atypical antipsychotics: NS BD taking lithium vs not: NS No association between WCST & clinical factors: age of onset, duration of illness, number of manic/depressive episodes, number of hospitalizations, or history of psychosis.
Ancín et al (2013)	148 BD	42.9 (11.6),	WAIS-R Digit Span	SCZ < BD < HC: Digit Span	Digit Span (forward)	Digit Span (backward)	<u>Clinical & demographic profiles</u>: % male: HC, BD < SCZ

	262 SCZ 108 HC (93 BDp, 55 BDnp)	60/88 37.1 (9.5), 185/77 42.2 (12.4), 54/54	VFT (FAS & animals) TMT A/B WCST SCWT TOH	(forward) SCZ, BD < HC: Digit Span (backward), VFT (animals), TMT A/B, WCST, SWCT, TOH SCZ < HC; BD < HC: VFT (FAS) NS: NA	VFT (FAS)	VFT (animals) TMT A/B WCST SCWT TOH	Age: SCZ < HC, BD Education years: SCZ < BD < HC IQ: SCZ, BD < HC PANSS & # antipsychotic drugs: BD < SCZ Age of onset, HDRS, illness duration, # antidepressive drugs: SCZ < BD <u>Association with cognitive score</u>: Employment status: Employed SCZ patients ↑ forward Unemployed < Employed (BD & SCZ), except 4-disks TOH Correlations in BD group: Digit span backward & SCWT: # depressive episode FAS: # depressive episode, illness duration Animals: illness duration, # depressive episodes, # drugs TMT A/B: illness duration, # drugs, # manic & depressive episodes WCST: # hospitalization, illness duration TOH: illness duration, # manic, depressive symptoms Correlations in SCZ group: Digit span, FAS: # drugs Animals, TMT A: illness

							duration, # drugs WCST: illness duration, # episodes, #hospitalization SCWT: illness duration, # drugs, # hospitalization TMT B: illness duration, # drugs, # episodes TOH: # hospitalization, illness duration Correlations with scores: YMRS: Animals HDRS: forward, VFT, TMT B, TOH PANSS: digit span, VFT, TMT A, WCST, SCWT
Arduini et al (2003)	22 BDp 42 SCZ 40 HC	36.7 (11.8), 12/10 37.4 (12.2), 26/16 Age NS, 20/20	WCST	SCZ < HC: perseverative errors, categories, total errors BD < HC: categories NS: unique errors		WCST (all subtests)	<u>Clinical & demographic profiles</u>: Sex, age, education years, illness duration, SAPS, SUMD: NS SANS: BD < SCZ <u>Association with cognitive score</u>: No association with insight
Barrett et al (2009)	32 BD 46 SCZ 67 HC	36.7 (9.3), 16/16 29.0 (9.9), 32/14 33.2 (10.9),	WMS Paired Associates WMS Digit Span COWAT	SCZ < HC: All measures BD < HC: All measures	All measures: low IQ SCZ < preserved IQ SCZ, BD	All measures when IQ and age were controlled for	<u>Clinical & demographic profiles</u>: Age: SCZ < BD Premorbid IQ SCZ vs BD: NS Current IQ SCZ < BD PANSS (+) SCZ vs BD: NS PANSS (-) & BDI: BD < SCZ

		39/28					Current IQ, PANSS (-) & depression correlated with each other <u>Association with cognitive score</u>: PANSS (-) & ↓ IQ: ↓ COWAT
Brissos et al (2008)	30 BD 23 SCZ 23 HC	36.3 (12.0), 15/15 36.6 (10.6), 16/7 36.6 (12.0), 4/19	WAIS-R Information WMS Logical Memory WMS Digit Span COWAT TMT A/B SDMT SCT/SCWT TOH	SCZ < BD < HC: SDMT SCZ, BD < HC: SCT (seconds), TMT A/B, TOH SCZ < BD, HC: SCWT NS: WAIS Information WMS Logical Memory WMS Digit Span COWAT	SDMT SCWT	WAIS Information WMS Logical Memory WMS Digit Span COWAT SCT TMT A/B TOH	<u>Clinical & demographic profiles</u>: % female: SCZ, BD < HC Age, education years: NS Age of onset, illness duration, # hospitalizations: NS PANSS: BD < SCZ YMRS, HDRS: HC < BD, SCZ QOL SCZ vs BD: NS <u>QOL and cognitive scores</u>: *In BD patients*: Physical domain (+) correlated with SDMT, (-) correlated with TMT A/B, TOH, SCT (errors). Social domain (-) correlated with TMT B. Psychological (-) correlated with TOH Environmental domain (-) correlated with TMT B, TOH, SCWT (errors) *In SCZ patients*: no correlations *In HC subjects*: Physical domain was (-) correlated with Digit Span.

							Psychological domain was (+) correlated with SCWT (errors)
Caletti et al (2013)	18 BD 30 SCZ 18 HC	42.2 (11.7), 4/14 42.5 (10.2), 24/6 36.1 (14.5), 6/12	BACS Verbal Memory BACS Digit Sequencing BACS Token Motor BACS Verbal Fluency BACS Symbol Coding BACS Tower of London	SCZ < HC: All BACS domains BD < HC: All BACS domains, except for Tower of London when substance abuse was controlled for	BACS Verbal Memory BACS Symbol Coding	BACS Digit Sequencing BACS Token Motor BACS Verbal Fluency BACS Tower of London	<u>Clinical & demographic profiles</u>: # males, history of substance abuse: BD, HC < SCZ Age, age of onset, illness duration, duration of untreated illness: NS GAF: SCZ < BD < HC <u>Association with cognitive score</u>: GAF was (+) correlated with all BACS domains, except Tower of London.
Cholet et al (2014)	42 BD 15 SCZ	70.2 (7.2), 14/28 68.8 (7.4), 5/10	BACS Verbal Memory BACS Digit Sequencing BACS Token Motor BACS Verbal Fluency	No HC recruited	BACS Verbal Memory BACS Token Motor	BACS Digit Sequencing BACS Verbal Fluency BACS Symbol Coding BACS Tower of London	<u>Clinical & demographic profiles</u>: Inclusion criteria: age ≥ 60 Age of onset, % lithium: SCZ < BD GAF: SCZ < BD I-ADL, S-ADL: BD < SCZ Hospitalization, education, ECT, suicide attempts, duration of employment: NS HDRS, MDRS, MAS, YMRS, PANSS total score, MMSE: NS

			BACS Symbol Coding BACS Tower of London TMT A/B			TMT A/B	Association with cognitive score: GAF (+) correlated with BACS I-ADL & S-ADL (-) correlated with BACS, except Digit Sequencing for I-ADL. BD only: Age did not affect scores. Education correlated with BACS total, verbal memory, working memory, verbal fluency & symbol coding. Early onset (-) correlated with token motor & Tower of London. Duration & # hospitalizations (-) correlated with BACS. BD subtypes not correlated. BD with lithium < without lithium; with ECT < without ECT for token motor task.
Depp et al (2007)	67 BD 150 SCZ 85 HC	57.6 (9.1), 48/19 57.4 (9.1), 100/50 64.2 (9.8), 35/50	CVLT Story memory WAIS Digit Span Grooved Pegboard VFT (FAS) TMT A/B WAIS-R Digit	SCZ < BD < HC: CVLT, TMT A/B, WAIS-R Digit Symbol SCZ, BD < HC: Story Memory WAIS Digit Span Grooved Pegboard VFT (FAS) WAIS-R Block Design WCST	CVLT TMT A/B WAIS-R Digit Symbol	Story Memory WAIS Digit Span Grooved Pegboard VFT (FAS) WAIS-R Block Design WCST	Clinical & demographic profiles: Age & % female: BD, SCZ < HC BPRS, PANSS: BD < SCZ HAM-D, age of onset, % comorbid substance abuse, # depressive symptoms, psychotic symptoms: NS 14 BD in partial or full remissions. 36% BD had concurrent psychotic features. Association with cognitive score: Education correlated with Digit

			Symbol WCST WAIS-R Block Design				Span No other correlations found
Dickerson et al (2001)	26 BD 74 SCZ	NA	RBANS Intermediate Verbal Memory RBANS Delayed Memory WAIS Letter Number Sequencing RBANS Attention TMT A	No HC recruited	RBANS Immediate Verbal Memory	RBANS Delayed Memory WAIS Letter Number Sequencing RBANS Attention TMT A	<u>Clinical & demographic profiles</u>: Age, gender, education level, illness duration, race, history of substance abuse, marital status, # hospitalization: NS PANSS (+), (-), Total: BD < SCZ, but not general psychopathology <u>Association with cognitive score</u>: Not discussed
Dickerson et al (2004)	117 BD 229 SCZ 100 HC	41.4 (12.2), 35/82 42.1 (9.5), 139/90 36.0 (12.3), 25/75	RBANS List Learning RBANS Story Memory Task RBANS Digit span RBANS Coding Task	SCZ < BD < HC for all measures	All measures		<u>Clinical & demographic profiles</u>: Age: HC < BD, SCZ % male: BD, HC < SCZ % Caucasian: HC < SCZ < BD Education years: SCZ < BD < HC # atypical antipsychotics, PANSS (+),(-), general symptoms and total scores: BD < SCZ Age at 1st hospitalization, duration since last hospitalization, age of onset: NS

							Association with cognitive score: Diagnosis of BD, more education years, Caucasian, lower PANSS (-) score & (-) seroreactivity to HSV-1 predicted 46% of variance of RBANS total score.
Frangou et al (2006)	43 BD 54 SCZ 46 HC (9 BDp, 34 BDnp)	42.7 (11.1), 20/23 39.1 (10.5), 43/11 42.7 (11.3), 21/25	VFT (FAS) VFT Category (animals, vegetables, fruits) SCWT WCST	BD < HC: Correct responses for VFT SCZ < HC: Correct responses for VFT, total # of errors in VFT category, SWCT in congruent & incongruent conditions BD ≈ HC: SWCT, WCST SCZ ≈ HC: WCST	Correct responses in VFT FAS & category # errors in VFT category Correct responses in congruent condition of SWCT	WCST Correct responses in incongruent condition of SWCT	Clinical & demographic profiles: IQ: SCZ, BD < HC % male, # typical/atypical antipsychotics: BD < SCZ # mood stabilizer, anticholinergics: SCZ < BD Age, age of onset, illness duration, #antidepressant, education years, history of psychotic features: NS Association with cognitive score: PANSS in SCZ; HAMD & MRS in BD not correlated with any scores. VFT: significant gender effect, but no gender-diagnosis interactions WCST: no gender or group effect SWCT: no gender & interaction effect , but significant group effect
Glahn et al (2006)	15 BDp	32.3 (10.6),	WAIS III Digit Span	SCZ < HC; SCZa < HC:		SCZa vs BDp: NS	Clinical & demographic profiles: Education years, IQ, GAF: SCZa

	11 BDnp 15 SCZa 15 SCZ 32 HC	4/11 35.4 (10.4), 3/8 36.4 (10.0), 6/9 37.5 (6.8), 8/7 39.0 (10.5), 13/19		Digit Span forward & backward BDp < HC; BDnp < HC: Digit Span backward only			< HC; SCZ < HC # hospitalizations: BDnp, BDp < SCZ < SCZa % atypical: BDnp < BDp, SCZa, SCZ Age, gender, parental education, age of onset, BPRS scores in SCZa & SCZ, YMRS scores in BDnp & BDp: NS <u>Association with cognitive score</u>: BDp vs BDnp: NS SCZa vs SCZ: NS HAMD, BPRS, YMRS not significantly related to working memory scores.
Gogos et al (2010)	16 BD male 24 BD female 24 SCZ male 14 SCZ female 21 HC male 22 HC	46(12) 40(11) 43(11) 42(13) 41(12) 41(11)	RBANS List Learning RBANS Story Memory Task RBANS Picture Naming, Semantic Fluency RBANS Digit Span, Coding	SCZ < HC: all measures BD < HC: RBANS List Learning, Story Memory Task, Picture Naming, Semantic Fluency; Digit Span & Coding on a trend.	RBANS List Learning RBANS Story Memory Task	RBANS Picture Naming Semantic Fluency RBANS Digit Span RBANS Coding	<u>Clinical & demographic profiles</u>: Gender, age, IQ: NS Age of onset: NS, but BD female had earlier age of onset compared to BD male patients. Illness duration, PANSS (+), general & total scores: NS PANSS (-), CPZ: BD < SCZ <u>Association with cognitive score</u>: RBANS Total: BD male < BD female Story memory: SCZ female > SCZ male Gender effect: semantic fluency & coding (Male < female)

	female						In SCZ, only general PANSS score correlated with RBANS Total score In BD, no correlations between RBANS Total & clinical measures
Hill et al (2013)	227 BDp 293 SCZ 55 SCZa (D) 110 SCZa (M) 295 HC	36.2 (12.8), 85/142 35.9 (12.8), 198/95 38.2 (11.9), 29/26 35.8 (11.7), 38/72 37.6 (12.6), 123/172	BACS Verbal Memory BACS Digit Sequencing BACS Token Motor BACS Verbal Fluency BACS Symbol Coding BACS Tower of London	SCZ, BDp < HC: All measures	SCZ < BDp; SCZ < SCZa < BDp: All measures		<u>Clinical & demographic profiles</u>: All patients had history of psychotic features. <u>Association with cognitive score</u>: Total BACS ↓ as affective features ↓ and psychosis ↑ SCZa depressed group vs SCZa manic group: NS Medications, history of substance abuse/dependence, side effects, & clinical ratings had minimal associations with BACS. BACS composite score correlated with social functions in SCZ & BD
Krabbendam et al (2000)	22 BD 22 SCZ 22 HC (12 BDp, 10	47.7 (8.3), 5/17 39.6 (6.6), 12/10 41.4 (11.3), 10/12	AVLT Word Fluency LDST SCWT color naming/reading	SCZ < HC: AVLT delayed & immediate recall, SCWT, all subtests of CST, LDST, word fluency BD < HC:	Not discussed	Not discussed	<u>Clinical & demographic profiles</u>: Age: SCZ, HC < BD IQ: SCZ < HC Gender, education level: NS <u>Association with cognitive score</u>: BD with lithium vs carbamazepine; BD I vs BD II;

	BDnp)		SCWT Interference Number/letter-trekking task of CST Number/letter-shifting task of CST	AVLT delayed & immediate recall, letter-tracking of CST, number/letter-switching of CST, LDST NS: AVLT Recognition			patients with vs without psychotic features: NS No correlations between cognitive scores with # of episodes & symptomatology ratings.
Kuswanto et al (2013)	42 BD 72 SCZ 49 HC (11 BDp, 31 BDnp)	32.6 (9.7), 17/25 31.5 (8.3), 38/34 31.9 (10.4), 28/21	BACS Verbal Memory BACS Digit Sequencing BACS Token Motor BACS Verbal Fluency BACS Symbol Coding BACS Tower of London	SCZ < HC: Verbal Memory, Digit Sequencing, Tokens left, Verbal Fluency, Symbol Coding, BACS Total BD < HC: Verbal Memory, Digit Sequencing, Tokens correct, Verbal Fluency, Symbol Coding, BACS Total NS: Tower of London		All measures	<u>Clinical & demographic profiles</u>: Education years: BD, SC < HC GAF, YMRS: SCZ < BD PANSS: BD < SCZ Age, father's education years, premorbid IQ, Illness duration, age of onsets, CPZ, gender: NS <u>Association with cognitive score</u>: BDp vs BDnp: NS ↓ GAF & older age predicted ↓ BACS total score. Diagnoses & CPZ not associated with BACS total score.
Lee et al (2013)	68 BD 38 SCZ	43.9 (10.6), 37/31	MCCB: Speed of processing,	SCZ, BD < HC: Reasoning/problem solving	Processing speed	Reasoning/problem solving	<u>Clinical & demographic profiles</u>: Education: SCZ < BD, HC BPRS, YMRS: BD < SCZ

	36 HC (15 BDp, 31 BDnp)	44.7 (9.1), 21/17 41.4 (9.9), 20/16	Attention/vigilance, Working memory, Verbal memory, Reasoning/problem solving	SCZ < BD, HC: Processing speed, verbal memory SCZ < BD < HC: Attention, working memory	Verbal memory Attention Working memory		Age, parental education, age of onset, HDRS: NS Most BD were euthymic <u>Association with cognitive score</u>: BD showed significantly better social cognition than nonsocial cognition, SCZ showed a significant reverse pattern. BD: no correlations between cognitive performances with clinical symptoms. BD I vs BD II, BDnp vs BDp, BD with vs no antipsychotic: NS
Lewandowski et al (2011)	31 BDp 25 SCZ 29 SCZa 20 HC	33.9 (11.6), 11/20 37.8 (11.4), 15/10 38.3 (9.1), 13/16 40.4 (8.7), 11/9	HVLT-R VFT (Category) TMT A/B SCT/SCWT	SCZa, SCZ, BDp < HC In all measures	SCZ < BDp, SCZa: TMT B	HVLT-R VFT TMT A SCT/SCWT	<u>Clinical & demographic profiles</u>: Education: BDp, SCZ < HC #hospitalization, %antidepressant: BDp < SCZ < SCZa CPZ: BDp < SCZ, SCZa % inpatients: SCZa < SCZ < BDp PANSS (-): BDp < SCZa < SCZ YMRS: SCZa, SCZ < BDp Age, gender, % antipsychotics, race, % mood stabilizer, PANSS (+) & general symptoms, MADRS: NS All patients had history of psychotic features. SCZa had bipolar subtype. All BD were manic or hypomanic. <u>Association with cognitive score</u>:

							↓ TMT B: ↑ age, ↓ education ↓ SCWT: ↑ age, ↓ education, female % inpatient setting & gender predicted verbal fluency (female < male) CPZ predicted TMT A score Diagnosis, YMRS, MADRS, PANSS (+) & general symptoms were not a significant predictor of any cognitive scores. PANSS (-) predicted SCWT, TMT B.
Martínez-Arán et al (2002)	49 BD 49 SCZ	38.1 (9.8), 20/29 30.4 (7.5), 38/11	WAIS Digit Span COWAT (FAS) TMT A/B WCST	No HC recruited	WCST (category)	WCST (perseverative errors) WAIS Digit Span TMT A/B COWAT (FAS)	<u>Clinical & demographic profiles</u>: Age, age of onset, education years, #suicide attempts: SCZ < BD Age at 1st hospitalization, % hospitalization, chronicity: NS GAF: SCZ < BD PANSS: BD < SCZ <u>Association with cognitive score</u>: In BD, verbal fluency was nearly significant as an indicator of good functional outcome (GAF) PANSS (-) & WCST preservative errors accounted for 40% of variance of GAF in SCZ patients.
McClellan et al (2004)	21 BD	15.3 (1.6), 13/8	CVLT – Children's version	No HC recruited		All measures	<u>Clinical & demographic profiles</u>: % antipsychotics:

	26 SCZ 19 Psychosis NOS	14.8 (2.2), 19/7 14.7 (2.7), 13/7	WISC-III/WAIS-R Digit Span COWAT (FAS) WCST				Psychosis NOS < BD < SCZ % lithium: SCZ, Psychosis NOS < BD % antidepressants: BD, SCZ < Psychosis NOS IQ, age, age of onset, gender, race, socioeconomic status, % anticonvulsant, % stimulant, % antianxiety: NS <u>Association with cognitive score</u>: Not discussed
Meesters et al (2013)	74 BD 47 SN 20 SR 69 HC	70.3 (7.1), 35/39 67.5 (7.1), 16/31 68.1 (8.4), 4/16 72.2 (8.3), 21/48	10 Words Test WAIS Digit Span Animal & letter naming TMT A/B SCWT Interference	SN, SR, BD < HC: 10 Words Test Animal & Letter naming TMT A/B SCWT SN, BD < HC: WAIS Digit Span (backward) BD < HC: WAIS Digit Span (forward)	SN < BD: 10 Words Test (Learning) Animal naming TMT A/B WAIS Digit Span (forward)	10 Words Test (Retention) Letter naming WAIS Digit Span (backward) SWCT SR vs BD: NS in all domains	<u>Clinical & demographic profiles</u>: Age: SC < HC Education: SN, SR < HC; SC < BD YMRS: SR, BD, HC < SN % antipsychotics: BD < SN, SR PANSS: SR < SN Premorbid IQ: SN < HC, BD Gender, age of onset, illness duration, # hospitalizations, % antidepressant: NS <u>Association with cognitive score</u>: In SCZ, remission status or PANSS total score had significant effect on neurocognitive performance. History of psychosis did not change much of the p-values.

Mojtabai et al (2000)	72 BDp 102 SCZ 49 MD	30.5 (9.8), 36/36 30.2 (8.1), 70/32 30.8 (9.3), 19/30	WMS-R Paired associates Sentence repetition Silly Sentences FTT COWAT WAIS-R Digit Symbol Symbol Digit Modalities TMT A/B SCWT	No HC recruited	WMS-R Paired associates Sentence repetition Silly Sentences COWAT TMT A/B WAIS-R Digit Symbol Symbol Digit Modalities SCWT	FTT	<u>Clinical & demographic profiles</u>: % male: BD, MD < SCZ Race: non-Caucasian < Caucasian Education: less than high school < high school Lifetime substance use, age: NS Illness duration: BD < MD < SCZ SAPS: MD < BD < SCZ SANS: BD < MD < SCZ All patients were 1st-admission patients with psychotic symptoms at the time of admission. <u>Association with cognitive score</u>: Age, race, education associated with cognitive scores. Medication status & duration of untreated symptoms not associated with cognitive scores. Discriminant function analysis revealed that Silly Sentences, Digit Symbol and Symbol Digit Modalities reliably distinguished among diagnostic groups.
Reichenberg et al (2009)	78 BDp 94 SCZ 15 SCZa 48 MD	29.0 (9.7), 39/39 28.9 (8.9), 66/28 24.8 (4.9), 7/8 29.1 (8.7), 18/30	WMS-R Paired Associates FTT Letter Fluency TMT A/B	No HC recruited	Before & after adjusting for IQ: WMS-R Paired associates Letter Fluency	After adjusting for IQ: FTT	<u>Clinical & demographic profiles</u>: Age, education level, social class, IQ: NS % male, GDS, SAPS, BPRS: SCZa, BDp, MD < SCZ SANS: BDp, MD < SCZa, SCZ All patients have a psychotic disorder.

			Symbol Digit Modalities Test WAIS-R Digit Symbol Coding SCWT WAIS-R Picture Completion		TMT A/B Symbol Digit Modalities Test WAIS-R Digit Symbol Coding SCWT WAIS-R Picture Completion		<u>Association with cognitive score</u>: BPRS, SAPS, HDS, & medication status not associated with cognitive domains for SCZ & BDp.
Rossell (2006)	48 BD 62 SCZ 48 HC	39.5 (10.8), 14/34 40.2 (11.1), 38/24 37.1 (11.4), 30/18	Semantic Fluency: animals, food, fear, happy Letter Fluency: F, A, M, S	SCZ < BD, HC: Semantic fluency: total, animals, fear SCZ < HC < BD: Semantic fluency: happy SCZ, BD < HC: Letter fluency	Semantic fluency: total, animals, fear, happy	Semantic fluency: food Letter fluency	<u>Clinical & demographic profiles</u>: NART IQ: SCZ < BD, HC % male: SCZ < HC Age, education years, age of onset, SAPS: NS SANS: BD < SCZ <u>Association with cognitive score</u>: In patients, semantic fluency correlated with delusion score of SAPS & alogia of SANS. Letter fluency correlated with alogia of SANS only.
Rossi et al (2000)	40 BD 66 SCZ 64 HC	35.7 (11.7), 26/14 33.1 (8.7), 38/28 26.4 (5.4),	WCST	SCZ < HC: WCST (category, total errors, unique errors) BD vs HC: NS	WCST (category, total errors, unique errors)	WCST (perseverative errors)	<u>Clinical & demographic profiles</u>: Age, education: HC < SCZ, BD CPZ, illness duration: BD < SCZ (p-value unknown) Age of onset: SCZ < BD (p-value unknown)

		30/34					<u>Association with cognitive score</u>: No significant correlations with clinical factors.
Sánchez-Sánchez-Morla et al (2009)	73 BD 89 SCZ 67 HC	43.5 (10.4), 30/43 38.7 (9.6), 60/28 43.8 (11.2), 31/36	CVLT WAIS-R Digit Span (backward) COWAT (FAS) Animal Naming CPT TMT B WCST TOH Stroop Interference	SCZ < BD < HC: CLVT (trial 5, total score) WAIS-R Digit Span TMT B SCZ, BD < HC: CVLT (short free recall, % retention short/long-term, long term recall, short/long cued-recall) COWAT (FAS) Animal Naming CPT (hits, reaction time) WCST TOH NS: CVLT (% forgotten), CPT (sensitivity)	CVLT (learning, recognition memory) TMT B WAIS-R Digit Span	CVLT (% retention, free & cued recall, forgetfulness, semantic strategy) WCST Stroop Interference CPT	<u>Clinical & demographic profiles</u>: Age: SCZ < BD, HC Education, premorbid IQ: BD, SCZ < HC Age of onset, QLS: SCZ < BD PANSS (+), (-), SDS: BD < SCZ MDRS: HC < BD < SCZ HDRS: HC < BD, SCZ <u>Association with cognitive score</u>: BDp vs BDnp: NS Illness duration correlated with executive functions & verbal memory. Verbal memory correlated with QLS & GAF scores. #hospitalizations, #depressive & manic episodes & SDS not correlated w cognitive domains.
Schretlen et al (2007)	66 BD	41.5 (11.5),	HVLT-R	SCZ < BD < HC: HVLT-R (Trial 1-	HVLT-R (Trial 1-3, delay)	BTA	<u>Clinical & demographic profiles</u>: Age: SCZ, BD < HC

	106 SCZ 316 HC	25/41 40.0 (11.1), 73/33 54.5 (18.6), 139/177	Grooved Pegboard Letter Word Fluency (S, P) Category Fluency (supermarket items, animals) TMT A/B CPT BTA WCST	3, delay recall) Grooved Pegboard Category Fluency TMT A/B WCST SCZ,BD < HC: HVLT-R (recognition) Letter Word Fluency CPT BTA	Grooved Pegboard Category Fluency TMT A/B WCST	CPT Letter Word Fluency HVLT-R (recognition)	%male, education, premorbid IQ: BD, NC < SCZ SANS, SAPS, % antipsychotics: BD < SCZ % antidepressants, % lithium, % anticonvulsant: SCZ < BD Age of onset, illness duration, # hospitalizations: NS <u>Association with cognitive score</u>: No diagnosis effect on cognitive domains. Diagnosis effect found on overall "elevation" of profiles.
Seidman et al (2002)	15 BD 87 SCZ 94 HC	40.7 (13.1), 7/8 43.3 (11.7), 68/19 42.3 (15.2), 43/51	WMS Logical Memory WAIS-R Digit Span WRAT-R Arithmetic WAIS-R Digit Symbol TMT A/B WCST	SCZ < BD < HC: All measures SCZ < HC: All measures BD < HC: All measures except WRAT-R Digit Span, WRAT-R Arithmetic	WAIS-R Digit Symbol TMT A/B WCST Visual-Verbal Test	WMS Logical Memory WAIS-R Digit Span WRAT-R Arithmetic	<u>Clinical & demographic profiles</u>: Education, IQ: SCZ < BD, HC Parental SES: BD < SCZ, HC Duration of hospitalization, CPZ, Psychosis-Motivation rating: BD < SCZ Age, premorbid IQ, race, age of onset, #hospitalizations: NS <u>Association with cognitive score</u>: No correlations between cognitive scores and antipsychotics dosage. MANOVA suggested similar profile pattern between SCZ & BD.

			Visual-Verbal Test				
Simonsen et al (2011)	75 BDp 61 BDnp 102 SCZ 27 SCZa 280 HC	35.7 (11.7), 36/39 36.0 (10.3), 24/37 32.4 (9.8), 62/40 33.7 (9.9), 8/19 35.9 (10.5), 136/144	WMS-III Logical Memory CVLT-II WAIS-III Digit Span WM-MA WAIS-III Digit Symbol D-KEFS Verbal Fluency	SCZ, SCZa, BDp < BDnp, HC: WMS-III Logical Memory D-KEFS Verbal Fluency (set shifting) SCZ < BDnp, HC & SCZa, BDp < HC: WAIS-III Digit Span WM-MA SCZ < BDp/np, HC; SCZa < BDnp, HC; BDp < HC: WAIS-III Digit Symbol CVLT-II (learning) SCZ, SCZa < BDnp, HC; BDp < HC: CVLT-II (recall) D-KEFS (semantic) SCZ, BDp < HC:	D-KEFS Verbal Fluency CVLT-II WAIS-III Digit Symbol	SCZ, SCZa, BDp: NS WMS-III Logical Memory SCZa vs BDp: NS WAIS-III Digit Span WM-MA	<u>Clinical & demographic profiles</u>: % male: HC, BDp/np, SCZa < SCZ Education, IQ: SCZ < BDp/np, HC YMRS: BDp < SCZ, SCZa PANSS (+): BDp/np < SCZ, SCZa PANSS (-): SCZa, BDp/np < SCZ GAF: SCZ, SCZa < BDp/np # depressive symptoms: SCZ < BD # hypomanic symptoms: SCZ, SCZa, BDp < BDnp # manic episode: SCZ < BDp # psychotic symptoms, # hospitalizations: BDnp < SCZ, SCZa, BDp Age, IDS-C, illness duration, % antidepressant, % combination therapy, % substance abuse: NS <u>Association with cognitive score</u>: Groups with history of psychosis performed poorer than the non-psychotic groups. (+) correlations with education & premorbid IQ in all domains. (-) correlations with age on CVLT-II & WAIS-III Digit

				D-KEFS (phonetic) BDnp vs HC: NS			Symbol. Male < female in all measures, except for WM-MA. In SCZ, (-) correlations found between PANSS (-) & Logical Memory, CVLT-II Learning, Digit Symbol, & semantic fluency. PANSS (+) correlated with WM-MA. Psychosis correlated with semantic fluency. In BD, PANSS (-) correlated with Digit Symbol & D-KEFS. Manic, psychosis & hospitalization (-) correlated with verbal learning & memory, digit symbol, digit span, WM-MA, D-KEFS set shifting & semantic fluency.
Smith et al (2009)	25 PMD 72 SCZ 72 HC	41.4 (9.7), 13/12 39.1 (12.1), 29/43 39.9 (13.3), 33/39	Episodic memory: WMS-III Immediate Recall WMS-III Logical Memory Working memory: WAIS-III Number-Letter Sequencing WAIS-III Spatial Span WAIS-III Digit Span CPT	SCZ, PMD < HC: All domains		SCZ vs PMD: all measures	<u>Clinical & demographic profiles</u>: Psychotic Mood Disorder (PMD): 7 BDp, 18 SCZa Age, age of onset, gender, SES, race, drug use/abuse: NS Alcohol abuse/dependence: SCZ < PMD (+) & disorganized symptoms: HC < SCZ, PMD (-) symptoms: HC < PMD < SCZ Premorbid IQ: SCZ < PMD, HC <u>Association with cognitive score</u>: In SCZ, (-) & disorganized symptoms (-) correlated with all

			Executive functions: TMT B Verbal Fluency WCST WAIS-III Matrix Reasoning subtest				domains. In PMD, (-) symptoms correlated with working & episodic memory.
Szoke et al (2008)	52 BDp 40 BDnp 48 SCZ 26 SCZa 48 HC	36.5 (10.7), 18/34 44.5 (9.4), 15/25 32.7 (8.9), 37/11 33.5 (9.4), 13/13 42.2 (13.2), 24/24	WCST TMT A/B (TMT B-A difference)	SCZ/SCZa < HC: All measures BDnp/BDp vs HC: NS	SCZ vs BDp & BDnp: WCST (perseverative errors)	TMT A/B	<u>Clinical & demographic profiles</u>: Age, % male, % high school completed: $p < .001$ <u>Association with cognitive score</u>: BDp vs BDnp: NS Continuum of severity: BDnp < BDp < SCZa < SCZ. Diagnosis & education significantly influenced WCST & TMT A/B. Age significantly influenced TMT only. Gender had no significant effect.
Varga et al (2007)	37 BD 32 SCZ 31 HC	40.6 (9.6), 15/22 36.0 (11.6), 18/15 39.0 (10.9), 18/13	AVLT WAIS Digit Span Grooved Pegboard TMT A/B WAIS Digit Symbol	SCZ, BD < HC: Grooved Pegboard TMT A/B BD < SCZ, HC: WCST (perseverative errors) SCZ < BD < HC:	AVLT WAIS Digit Symbol Stroop Color	WAIS Digit Span Grooved Pegboard TMT A/B SWCT WCST	<u>Clinical & demographic profiles</u>: Education, IQ, employment: HC < BD < SCZ GAF: SCZ < BD BPRS, MADRS, CGI, , MRS of SADS-C, SUMD awareness, SUMD misattribution: BD < SCZ Age, gender, # hospitalizations, age of onset, illness duration, SUMD general: NS

			WCST Stroop Color SWCT	AVLT WAIS Digit Symbol Stroop Color NS: WAIS Digit Span WCST (category)			<u>Association with cognitive score</u>: Insight correlated with GAF, BPRS, MRS & CGI. In SCZ, SUMD awareness (-) correlated with TMT A/B, Stroop Color/SWCT, AVLT learning & IQ In BD, SUMD general (-) correlated with digit span & Grooved Pegboard; SUMD awareness with digit span.
Verdoux & Liraud (2000)	33 BD 20 SCZ 19 MD 29 psychotic disorders (29 BDp, 4 BDnp)	All subjects: 34.5 (10.5), 48/53	BEM-84 WCST SWCT	No HC recruited	BEM-84 (total score, history immediate recall)	BEM-84 (list of words immediate & delayed recall, history delayed recall) WCST SCWT	<u>Clinical & demographic profiles</u>: Psychotic disorders include SCZa, delusional disorder, NOS psychotic disorder. 8 MD patients had a history of psychotic features. Age, gender, education, age of onset, age at 1st admission: NS <u>Association with cognitive score</u>: No association between duration of illness and neurocognitive performance.
Zabala et al (2010)	19 BD 36 SCZ 52 psychosis	15.7 (1.9), 12/7 15.6 (1.8), 28/8 15.4 (1.7), 31/21	Working memory: WAIS-III Digits (backward) WAIS Number Letter Sequencing	Patients < HC: All domains		BD vs SCZ vs NOS: All domains	<u>Clinical & demographic profiles</u>: Parental SES: patients < HC PANSS (-) symptoms: BD < SCZ Age, education, gender, race, CPZ, PANSS (+) & general scores: NS

	NOS 98 HC	15.2 (1.9), 62/36	Attention: WAIS-III Digits (forward) TMT A (time) Stroop Colors/Word CPT Executive functions: TMT B FAS/COWAT (animal) Stroop Interference WCST				<u>Association with cognitive score</u>: (-) correlations between PANSS total score with attention domain. No correlations between PANSS & working memory & executive functions. No correlations between CPZ & all domains.
Zanelli et al (2010)	37 BD 65 SCZ 46 psychosis NOS 39 DP 177 HC	28.1 (8.1), 15/22 26.5 (8.4), 42/23 29.0 (9.6), 28/18 37.0 (12.9), 16/23 37.2 (12.9), 77/100	Verbal memory: RAVLT Executive functions & working memory: TMT B Letter-Number Span Test Raven's CPM Attention & speed of processing: TMT A WAIS-R Digit Symbol	*Before controlling for current IQ:* SCZ, psychosis NOS, DP < HC: All domains BD < HC: RAVLT, WAIS-R Verbal Fluency (category only) BD ≈ HC: Letter-Number Span Test, TMT A/B, Verbal Fluency (letter)	Letter-Number Span Test WAIS-R Digit Symbol	*After controlling for current IQ:* All domains	<u>Clinical & demographic profiles</u>: Age: patients < HC % male: BD, psychosis NOS, DP, HC < SCZ Education: group effect ($p < .01$) Race: NS Current IQ: SCZ, psychosis NOS, DP < HC; SCZ < BD Premorbid IQ: SCZ, psychosis NOS < HC; SCZ < BD <u>Association with cognitive score</u>: (-) symptoms associated with digit symbol, Raven's CPM, TMT A/B, RAVLT, categorical & letter fluency. Severity of reality distortion

			Verbal fluency: WAIS-R Verbal Fluency (semantic: body parts, fruits, animals; letters: F, A, S)	*After controlling for current IQ:* Patients < HC: RAVLT, Letter-Number Span Test, WAIS-R Verbal Fluency. NS: TMT A/B, Raven's CPM, Digit Symbol			associated with ↓ TMT B score. Severity of depressive symptoms not associated with any domains.

Abbreviations: AVLT, Auditory-Verbal Learning Test; BACS, The Brief Assessment of Cognition in Schizophrenia; BD, bipolar disorder; BDnp, bipolar disorder without psychotic features; BDp, bipolar disorder with psychotic features; BPRS, Brief Psychiatric Rating Scale; COWAT, Controlled Oral Word Association Test; COWAT (FAS), Controlled Oral Word Association Test FAS; CPZ, chlorpromazine; CST, computerized self test; CVLT, California Verbal Learning Test; D-KEFS, CVLT-II, California Verbal Learning Test - Second Edition; Delis-Kaplan Executive Function System; ECT, electroconvulsive therapy; F, female; FAS, Verbal fluency test FAS, FTT, Finger-tapping test; GAF, Global Assessment of Functioning; HAM-D, The Hamilton Rating Scale for Depression; HC, healthy controls; HDRS, Hamilton Depression Rating Scale; HDS, Hamilton Depression Scale; HVLT-R, Hopkins Verbal Learning Test-Revised; I-ADL, Instrumental Activities of Daily Living; IDS-C, Inventory of Depressive Symptoms – Clinician Rating; IQ, intelligence quotient; LDST, Letter-Digit Substitution Test; M, male; MADRS, Montgomery- Åsberg Depression Rating Scale; MANOVA, multivariate analysis of variance; MAS, Bech-Rafaelson Mania Scale; MCCB, MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) Consensus Cognitive Battery; MD, major depressive disorder; MMSE, Mini Mental State Examination; NS, not significant; PANSS, Positive and Negative Syndrome Scale; PMD, Psychotic Mood Disorder; Psychosis NOS, Psychosis disorder not otherwise specified; Raven's CPM; Raven's Coloured Progressive Matrices; RAVLT, Rey Auditory Verbal Learning Test; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; SANS, Scale for the Assessment of Negative Symptoms; QLS, Quality of Life Scale; QOL, Quality of Life; SAPS, Scale for the Assessment of Positive Symptoms; S-ADL, Social Activities of Daily Living; SCZa, schizoaffective disorder; SCT, Stroop Color Test; SCWT, Stroop Word-Color Test; SCZ, schizophrenia; SD, standard deviation; SDMT, Symbol Digit Modalities Test; SDS, Sheehan Disability Scale; SES, socio-economic statu; SR, Remitted schizophrenia patients; SUMD, Scale to Assess Unawareness of Mental Disorder; TMT A, Trail

Making Test A; TMT B, Trail Making Test B; TOH, Tower of Hanoi; VFT, Verbal fluency test; VFT (FAS), Verbal fluency test (FAS); WAIS, Weschler Adult Intelligence Scale; WAIS-III, Weschler Adult Intelligence Scale - Third Edition; WAIS-R, Weschler Adult Intelligence Scale - Revised Edition; WCST, Wisconsin Card Sorting Test; WM-MA, Working Memory-Mental Arithmetic Test 2-back; WMS, Weschler Memory Scale; WMS-R, Weschler Memory Scale-Revised; YMRS, Young Mania Rating Scale

Table 2

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Table 2: Summary of main findings for each neurocognitive domain

Cognitive domains	**SCZ < BD**	**SCZ ≈ BD**
Verbal memory	Barrett et al (2009): WMS Paired Associates Caletti et al (2013): BACS Verbal Memory Cholet et al (2014): BACS Verbal Memory Depp et al (2007): CVLT Dickerson et al (2001): RBANS Intermediate Verbal Memory Dickerson et al (2004): RBANS List Learning, Story Memory Task Gogos et al (2010): RBANS List Learning, Story Memory Task Hill et al (2013): BACS Verbal Memory Lee et al (2013): MCCB Verbal Memory Meesters et al (2013): (SN < BD) 10 Words Test (learning) Mojtabai et al (2000): WMS-R Paired associates, Sentence repetition, Silly Sentences	Altshuler et al (2004): CVLT Brissos et al (2008): WAIS-R Information, WMS Logical Memory Depp et al (2007): Story Memory Dickerson et al (2001): RBANS Delayed Memory Kuswanto et al (2013): BACS Verbal Memory Lewandowski et al (2011): HVLT-R McClellan et al (2004): CVLT – Children's Version Meesters et al (2013): 10 Words Test (retention) Sánchez-Morla et al (2009): CVLT (% retention, free & cued recall, forgetfulness, semantic strategy) Schretlen et al (2007): HVLT-R (recognition) Seidman et al (2002): WMS Logical Memory

	Reichenberg et al (2009): WMS-R Paired Associates Sánchez-Morla et al (2009): CVLT (learning, recognition memory) Schretlen et al (2007): HVLT-R (Trial 1-3, delay recall) Varga et al (2007): AVLT Verdoux & Liraud (2000): BEM-84 (total score, history immediate recall)	Simonsen et al (2011): WMS-III Logical Memory (SCZ vs SCZa vs BDp: NS) Smith et al (2009): WMS-III Immediate Recall, WMS-III Logical Memory (SCZ ≈ SCZa/BDp) Verdoux & Liraud (2000): BEM-84 (list of words immediate & delayed recall, history delayed recall) Zanelli et al (2010): RAVLT *(after controlling for current IQ)*
Working memory	Ancín et al (2013): Digit Span (forward) Barrett et al (2009): WMS Digit Span Hill et al (2013): BACS Digit Sequencing Lee et al (2013): MCCB Working Memory Meesters et al (2013): (SN < BD) WAIS Digit Span (forward) Sánchez-Morla et al (2009): WAIS-R Digit Span Zanelli et al (2010): Letter-Number Span	Ancín et al (2013): Digit Span (backward) Brissos et al (2008): WMS Digit Span Caletti et al (2013): BACS Digit Sequencing Cholet et al (2014): BACS Digit Sequencing Depp et al (2007): WAIS Digit Span Dickerson et al (2001): WAIS Letter Number Sequencing Glahn et al (2006): WAIS-III Digit Span (SCZa vs BDp)

	(*before controlling for current IQ*)	Kuswanto et al (2013): BACS Digit Sequencing Martínez-Arán et al (2002): WAIS Digit Span McClellan et al (2004): WISC-III/WAIS-R Digit Span Meesters et al (2013): WAIS Digit Span (backward) Seidman et al (2002): WAIS-R Digit Span, WRAT-R Arithmetic Simonsen et al (2011): WAIS-III Digit Span, WM-MA (SCZa vs BDp: NS) Smith et al (2009): WAIS-III Number-Letter Sequencing, WAIS-III Spatial Span, WAIS-III Digit Span, CPT (SCZ ≈ SCZa/BDp) Varga et al (2007): WAIS Digit Span Zabala et al (2010): WAIS-III Digits (backward), WAIS Number Letter Sequencing Zanelli et al (2010): Letter-Number Span (*after controlling for current IQ*)
Motor speed	Cholet et al (2014):	Caletti et al (2013):

	BACS Token Motor Task Hill et al (2013): BACS Token Motor Task Schretlen et al (2007): Grooved Pegboard	BACS Token Motor Task Depp et al (2007): Grooved Pegboard Kuswanto et al (2013): BACS Token Motor Task Mojtabai et al (2000): FTT Reichenberg et al (2009): FTT Varga et al (2007): Grooved Pegboard
Verbal fluency	Ancín et al (2013): VFT (FAS) Barrett et al (2009): COWAT Frangou et al (2006): VFT (FAS) & category Hill et al (2013): BACS Verbal Fluency Meesters et al (2013): (SN < BD) Animal naming Mojtabai et al (2000): COWAT Reichenberg et al (2009): Letter Fluency	Altshuler et al (2004): VFT Ancín et al (2013): VFT (animals) Brissos et al (2008): COWAT Caletti et al (2013): BACS Verbal Fluency Cholet et al (2014): BACS Verbal Fluency Depp et al (2007): VFT (FAS) Gogos et al (2010):

	Rossell (2006): Semantic fluency (total, animals, fear, happy) Schretlen et al (2007): Category fluency (supermarket items, animals) Simonsen et al (2011): D-KEFS	RBANS Picture Naming, RBANS Semantic Fluency Kuswanto et al (2013): BACS Verbal Fluency Lewandowski et al (2011): VFT (category) Martínez-Arán et al (2002): COWAT (FAS) McClellan et al (2004): COWAT (FAS) Meesters et al (2013): Letter naming Rossell (2006): Semantic fluency (food), letter fluency (F, A, M, S) Schretlen et al (2007): Letter Word Fluency (S, P) Zanelli et al (2010): WAIS-R Verbal Fluency (semantic: body parts, fruits, animals; letters; F, A, S) *(after controlling for current IQ)*
Attention & processing speed	Brissos et al (2008): SDMT Caletti et al (2013): BACS Symbol Coding Depp et al (2007): WAIS-R Digit Symbol, TMT A	Ancín et al (2013): TMT A Brissos et al (2008): TMT A Cholet et al (2014): BACS Symbol Coding, TMT A

	Dickerson et al (2004): RBANS Digit span, RBANS Coding Task Hill et al (2013): BACS Symbol Coding Lee et al (2013): MCCB Attention, MCCB Speed of Processing Meesters et al (2013): (SN < BD) TMT A Mojtabai et al (2000): TMT A, WAIS-R Digit Symbol, Symbol Digit Modalities Reichenberg et al (2009): TMT A, WAIS-R Digit Symbol, Symbol Digit Modalities Schretlen et al (2007): TMT A Seidman et al (2002): TMT A, WAIS-R Digit Symbol Simonsen et al (2011): WAIS-III Digit Symbol Varga et al (2007): WAIS Digit Symbol, Stroop Color Zanelli et al (2010): WAIS-R Digit Symbol (*before controlling for current IQ*)	Dickerson et al (2001): RBANS Attention, TMT A Gogos et al (2010): RBANS Digit Span, RBAN Coding Kuswanto et al (2013): BACS Symbol Coding Lewandowski et al (2011): TMT A Martínez-Arán et al (2002): TMT A Sánchez-Morla et al (2009): CPT Schretlen et al (2007): BTA, CPT Varga et al (2007): TMT A Zabala et al (2010): Attention domain (WAIS-III Digits (forward), TMT A Stroop Colors/Word, CPT) Zanelli et al (2010): WAIS-R Digit Symbol, TMT A (after *controlling for current IQ*)

Executive functions	Altshuler et al (2004): TMT B, WCST categories Brissos et al (2008): SCWT Depp et al (2007): TMT B Frangou et al (2006): SCWT in congruent condition Hill et al (2013): BACS Tower of London Lewandowski et al (2011): TMT B Martínez-Arán et al (2002): WCST (category) Meesters et al (2013): (SN < BD) TMT B Mojtabai et al (2000): TMT B, SCWT Reichenberg et al (2009): TMT B, SCWT, WAIS-R Picture Completion Rossi et al (2000): WCST (category, unique & total errors) Sánchez-Morla et al (2009): TMT B	Altshuler et al (2004): TMT A, WCST perseverative errors, SWCT Ancín et al (2013): TMT B, WCST, SCWT, TOH Arduini et al (2003): WCST Brissos et al (2008): SCT, TMT B, TOH Caletti et al (2013): BACS Tower of London Cholet et al (2014): BACS Tower of London, TMT B Depp et al (2007): WCST, WAIS-R Block Design Frangou et al (2006): WCST, SCWT incongruent condition Kuswanto et al (2013): BACS Tower of London Lee et al (2013): MCCB Reasoning/Problem Solving Lewandowski et al (2011): SCT/SCWT Martínez-Arán et al (2002): TMT B, WCST (perseverative errors)

	Schretlen et al (2007): TMT B, WCST Seidman et al (2002): TMT B, WCST, Visual-Verbal Test Szoke et al (2008): WCST (perseverative errors)	McClellan et al (2004): WCST Meesters et al (2013): SWCT Interference Rossi et al (2000): WCST (perseverative errors) Sánchez-Morla et al (2009): WCST, Stroop Interference Smith et al (2009): TMT B, Verbal Fluency, WCST, WAIS-III Matrix Reasoning subtest (SCZ ≈ SA/BDp) Szoke et al (2008): TMT B-A Difference Varga et al (2007): TMT B, SWCT, WCST Verdoux & Liraud (2000): WCST, SCWT Zabala et al (2010): Executive function domain (TMT B, FAS/COWAT (animal), Stroop Interference, WCST) Zanelli et al (2010): TMT B, Raven's CPM *(after controlling for current IQ)*

Abbreviations: AVLT, Auditory-Verbal Learning Test; BACS, The Brief Assessment of Cognition in Schizophrenia; BD, bipolar disorder; BDP, bipolar disorder with psychotic features; BEM-84, Battery of memory efficiency 84 items; BTA, Brief Test of Attention; COWAT, Controlled Oral Word Association Test; CPT, Continuous Performance Test; CVLT, California Verbal Learning Test; D-KEFS, Delis-Kaplan Executive Function System; FTT, Finger-tapping test; HVLT, Hopkins Verbal Learning Test; HVLT-R, Hopkins Verbal Learning Test-Revised; MCCB, MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) Consensus Cognitive Battery; RAVLT, Rey Auditory Verbal Learning Test; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; SA, schizoaffective disorder; SCT, Stroop Color Test; SCWT, Stroop Word-Color Test; SCZ, schizophrenia; SDMT, Symbol Digit Modalities Test; SN, non-remitted schizophrenia patients; TMT A, Trail Making Test A; TMT B, Trail Making Test B; VFT (FAS), Verbal fluency test (FAS); WAIS, Weschler Adult Intelligence Scale; WAIS-III, Weschler Adult Intelligence Scale - Third Edition; WAIS-R, Weschler Adult Intelligence Scale - Revised Edition; WCST, Wisconsin Card Sorting Test; WISC-III, Weschler Intelligence Scale for Children-Third Edition; WMS, Weschler Memory Scale; WMS-III, Weschler Memory Scale-Third Edition; WMS-R, Weschler Memory Scale-Revised; WRAT-R, Wide Range Achievement Test

Table 3

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Table 3. Neurocognitive tests administered in extant studies

Verbal Memory	Working Memory	Motor Speed	Verbal Fluency	Attention/Speed of Processing	Executive Functions
CVLT WMS Paired Associates WAIS-R Information WMS Logical Memory Story Memory RBANS Intermediate Verbal Memory RBANS Delayed Memory RBANS List Learning RBANS Story Memory Task BACS Verbal Memory AVLT MCCB Verbal Learning HVLT-R 10 Words Test BEM-84 RAVLT	WAIS-R Digit Span WMS Digit Span WAIS Letter Number Sequencing RBANS Digit Span RBANS Coding Task (together with Attention) WAIS-III Digit Span BACS Digit Sequencing MCCB Working Memory WRAT-R Arithmetic WM-MA WAIS-III Spatial Span Letter-Number Span Test	Grooved Pegboard BACS Motor Token Task FTT	VFT FAS/Animals or other categories COWAT RBANS Semantic Fluency RBANS Picture Naming Task BACS Verbal Fluency (FS and category: supermarket items) D-KEFS Verbal Fluency	TMT A SDMT WAIS-R Digit Symbol WAIS-III Digit Symbol RBANS Attention RBANS Digit Span BACS Symbol Coding Letter Digit Substitution Test MCCB Attention & Processing Speed CPT	TMT B WCST SCWT SCT TOH WAIS-R Block Design BACS Tower of London MCCB Reasoning/Problem Solving WAIS-III Matrix Reasoning subtest Raven's CPM

Abbreviations: AVLT, Auditory-Verbal Learning Test; BACS, The Brief Assessment of Cognition in Schizophrenia; BEM-84, Battery of memory efficiency 84 items; COWAT, Controlled Oral Word Association Test; CVLT, California Verbal Learning Test; D-KEFS, Delis-Kaplan Executive Function System; FTT, Finger-tapping test; HVLT, Hopkins Verbal Learning Test; MCCB, MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) Consensus Cognitive Battery; Raven's CPM; Raven's Coloured Progressive Matrices; RAVLT, Rey Auditory Verbal Learning Test; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; SCT, Stroop Color Test; SCWT, Stroop Word-Color Test; SDMT, Symbol Digit Modalities Test; TMT A, Trail Making Test A; TMT B, Trail Making Test B; TOH,

Tower of Hanoi; VFT FAS, Verbal fluency test FAS; WAIS, Weschler Adult Intelligence Scale; WAIS-III, Weschler Adult Intelligence Scale - Third Edition; WAIS-R, Weschler Adult Intelligence Scale - Revised Edition; WCST, Wisconsin Card Sorting Test; WM-MA, Working Memory-Mental Arithmetic Test 2-back; WMS, Wechsler Memory Scale; WRAT-R, Wide Range Achievement Test

Figure 1

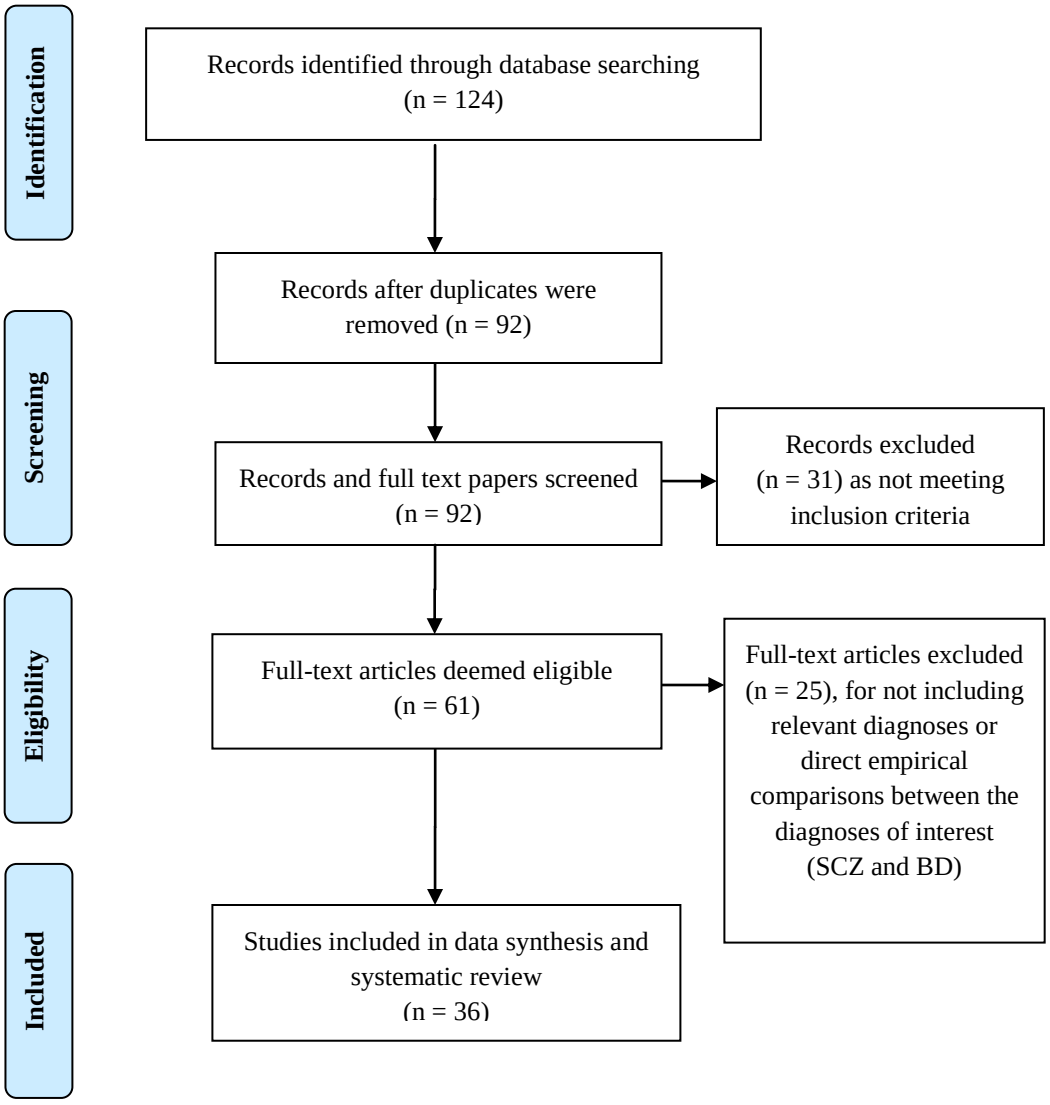

Figure 1. PRISMA flowchart illustrating methodological steps in identifying empirical studies that were included in this systematic review.