Systematic Review of Cognitive Function in Euthymic Bipolar Disorder and Pre-Surgical Temporal Lobe Epilepsy

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Background: Bipolar disorder (BD) and temporal lobe epilepsy (TLE) overlap in domains including epidemiology, treatment response, shared neurotransmitter involvement and temporal lobe pathology. Comparison of cognitive function in both disorders may indicate temporal lobe mediated processes relevant to BD. This systematic review examines neuropsychological test profiles in euthymic bipolar disorder type I (BD-I) and pre-surgical TLE and compares experimental designs used.

Methods: A search of PubMed, PsychINFO, and Scopus using Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines was conducted. Inclusion criteria were comparison group or pre- to post-surgical patients; reported neuropsychological tests; participants aged 18–60 years. Fifty six studies met criteria: 27 BD-I; 29 TLE.

Results: Deficits in BD-I compared to healthy controls (HC) were in executive function, attention span and verbal memory. Deficits in TLE compared to HC were in executive function and memory. In the pre- to post-surgical comparisons, verbal memory in left temporal lobe (LTL) and, less consistently, visuospatial memory in right temporal lobe (RTL) epilepsy declined following surgery. BD-I studies used comprehensive test batteries in well-defined euthymic patients compared to matched HC groups. TLE studies used convenience samples pre- to post-surgery, comparing LTL and RTL subgroups, few included comparisons to HC (5 studies). TLE studies typically examined a narrow range of known temporal lobe-mediated neuropsychological functions, particularly verbal and visuospatial memory.

Conclusion: Both disorders exhibit deficits in executive function and verbal memory suggestive of both frontal and temporal lobe involvement. However, deficits in TLE are measured pre- to post-surgery and not controlled at baseline pre-surgery. Further research involving a head-to-head comparison of the two disorders on a broad range of neuropsychological tests is needed to clarify the nature and extent of cognitive deficits and potential overlaps.

Keywords: bipolar disorder, temporal lobe, focal seizures neuropsychology, cognition, epilepsy, systematic review

INTRODUCTION

Bipolar disorder type I (BD-I) is typically characterized by episodes of mania and depression with inter-episode euthymia. A number of impairments have been noted in the euthymic phase of the illness including social, occupational functioning, and cognitive deficits [1, 2].

Most studies have examined cognitive deficits in euthymic patients with BD-I compared to healthy controls (HC). Five meta-analyses have reported impairments in cognitive domains of executive functioning [3–7], verbal memory [3, 5–7], visuospatial memory [7], and attention [4, 6]. One meta-analysis found no impairment of verbal memory and executive function in BD-I compared to HC [8]. An individual patient data meta-analysis by Bourne et al. [9] reported impaired verbal memory and attention in euthymic BD-I patients relative to HC [9]. The absence of an association between cognitive impairment and medication dose in euthymic BD-I patients suggest the effects of medication do not fully account for the cognitive impairments observed [4]. These meta-analyses support the assumption that cognitive impairments exhibited in the euthymic phase are trait markers of the disorder.

An alternate research design is to compare and contrast cognitive deficits in BD-I to a reference condition which shares common features. For example, a meta-analysis comparing BD-I and schizophrenia reported more pronounced cognitive deficits in schizophrenia on measures of verbal fluency, verbal memory, executive function, visuospatial memory, mental speed, IQ, and concept formation [10]. Similarly a single study comparing BD-I, obsessive compulsive disorder reported impaired verbal and episodic memory compared to HC [11]. The BD-I group had greater impairments in learning word lists and delayed recall. These results suggest the importance of the temporal lobes in both disorders in the consolidation and retrieval of memories.

A single study compared BD-I with complex partial seizure disorder [12]. It is noted that the classification of epilepsy syndromes has been subject to a number of iterations. In this review, we use the most commonly reported and widely understood term "temporal lobe epilepsy (TLE)" to incorporate the terms complex partial seizure disorder and focal seizures arising from the temporal lobes. The Jones et al. study reported greater impairment of executive function, attention and delayed verbal recall in the TLE group. These results should be interpreted with caution given the small and unequal sample sizes (BD-I $n = 26$, TLE $n = 9$). A case can be made for further exploration of similarities and differences between the neuropsychological test profiles seen in euthymic BD-I and interictal TLE. This is particularly so given the localizing pathology of TLE, which allows inferences to be made regarding the contribution of temporal lobe processes to the range of cognitive deficits reported in BD-I.

There are a number of established similarities between BD-I and TLE. These typically include a chronic course punctuated by episodic manifestations of mania and seizures, respectively. Other similarities include: the proposed involvement of kindling mechanisms [13]; changes in neurotransmitters (excitatory amino acids, GABA, dopamine and serotonin), voltage-opened ion channels (sodium, calcium and potassium) and second messenger systems (G-proteins, phosphatidylinositol, protein kinase C, myristoylated alanine-rich C kinase substrate), and treatment response to antiepileptic medications in both disorders [14].

In addition, episodes in both disorders commonly feature sensory, perceptual, cognitive, and affective changes [15] including depression [16]. Epidemiological studies have shown that the proportion of BD-I among people with epilepsy is more than twice as high as in the general population [17] and that mania is more common in patients with TLE than in the general population [18]. BD-I is also associated with comorbid epilepsy but not parental epilepsy [19]. Episodes of mania in BD-I and seizures in TLE share precipitating factors including stress, sleep reduction and antidepressant medications [20].

The temporal lobes have also been the subject of neuroimaging research in both disorders. In BD-I many studies have investigated correlates of the disorder to specific brain regions. Meta-analyses of magnetic resonance imaging (MRI) studies have reported that BD-I is associated with right lateral ventricular enlargement [21] and an enlarged left amygdala [22]. However, studies of temporal lobe size are inconsistent; with reported increases [23], reductions [24] or no differences [25–28] likely reflecting the difficulties of defining and measuring the volume of individual cerebral lobes on MRI.

In TLE, MRI studies have reported structural brain abnormalities in the hippocampus, entorhinal cortex [29], thalamus [30], and fornix [31]. On voxel-based morphometry, TLE is associated with gray matter pathology in the hippocampus, cingulum, thalamus, and frontal lobes. White matter reductions ipsilateral to the seizure focus were also found in the temporopolar, entorhinal, and perirhinal areas [32]. Typically, TLE originates unilaterally from the medial temporal lobe; they may, however, be propagated from other regions which project to limbic areas [33].

Given these potential diffuse structural abnormalities seen in patients with TLE, it could be expected that neuropsychological deficits may not be limited to tasks involving temporal lobe function. Patients with TLE display deficits in memory, general intelligence, language, executive function, and motor speed relative to HC [34, 35]. Deficits in verbal memory, language, and psychomotor speed may be affected by factors such as age of onset of epilepsy, general intelligence, the number and dose of antiepileptic medications used, and seizure frequency [35].

The literature describing clinical features, imaging findings, and neuropsychological test profiles is largely in a separate corpus for BD-I and for TLE with only one small study directly comparing the two [12].

The current structured review brings these two bodies of work together in a comparison of the neurocognition literature findings of the two conditions side-by-side. The aim is to determine whether and to what extent the cognitive impairments seen in euthymic BD-I are mirrored by those attributed to a pathology primarily affecting the temporal lobes, that is TLE.

METHOD

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [36].
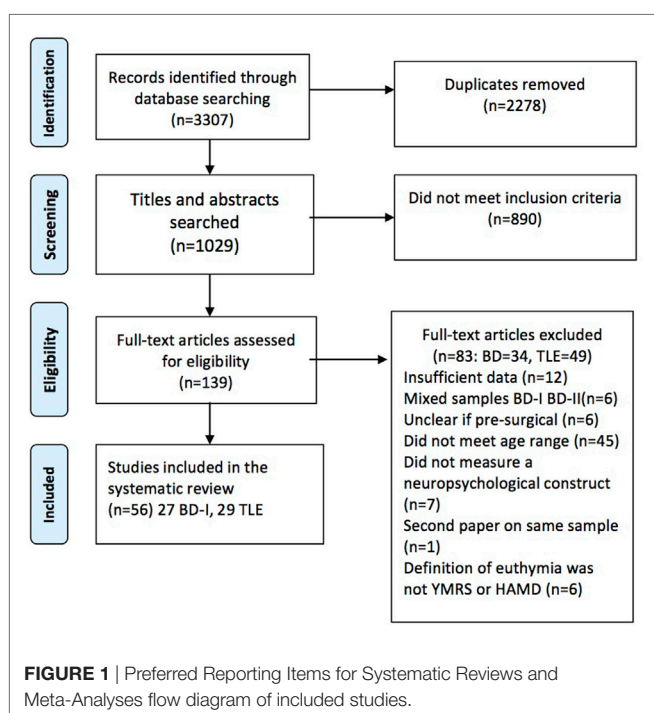
Inclusion criteria: (a) controlled comparison, (b) patients diagnosed with BD-I as assessed by a recognized criterion-based diagnostic system, (c) BD-I patients rated as euthymic, defined by their scores on a rating scale (<8 HamD, <8 YMRS); patients with unilateral TLE, from any cause, with diagnosis confirmed in a pre-surgical workup, (d) at least one neuropsychological test, (e) adult participants (18–60 years), (f) in the case of more than one article by the same authors results were not identified as being from the same sample, (f) articles published 1980 or later.

Identification of Studies

A comprehensive search of the electronic databases PubMed, PsychINFO, and Scopus for peer-reviewed articles published in English was conducted in the last week of May 2016. Search terms were grouped as follows: bipolar, manic depress*, baseline, asympt*, remit*, stable (group 1); or epilep*, seizure, presurg*, temporal, focal, partial, complex, interictal (group 2) and WAIS, Wechsler, trail making, continuous performance, stroop, digit span, verbal learning, rey, working memory, benton, card sort*, verbal fluency, RAVLT, CAVLT, tower of London (group 3). These search terms were combined as follows: group 1 AND group 3 for BD-I and group 2 AND group 3 for TLE.

Data Extraction

The abstracts located from the search strategy were entered into EndNoteX7. The PRISMA flowchart (**Figure 1**) sets out the steps in screening conducted by author EB. After the screening of titles and abstracts the remaining 139 studies were examined in full text, using a purpose built coding sheet to assess whether they met inclusion criteria. This process resulted in the study sample of 56, of which 27 related to BD-I and 29 to TLE.

FIGURE 1 | Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of included studies.

RESULTS

The search strategy identified an initial 3,307 articles of which 56 met inclusion criteria, 27 related to BD-I and 29 to pre-surgical TLE. Studies of BD-I are summarized in **Table 1** and of TLE in **Table 2** detailing authors, sample sizes, medication (BD-I only as this was not recorded in the TLE samples), neuropsychological test parameters, and summary results.

As demonstrated in **Table 1**, 25 of 27 studies compared patients with BD-I ($n = 1,398$) to HC ($n = 1,142$). The remaining studies compared manic, euthymic, and depressed groups. The most commonly reported impairments in BD-I were in executive function, attention span, and verbal memory. No studies found enhanced neuropsychological function in euthymic BD-I.

As shown in **Table 2**, in the epilepsy literature, all of the TLE studies compared neuropsychological test performance pre- to post-surgery. Only 5 of the 29 studies compared pre-surgical TLE ($n = 150$) to HC ($n = 111$); these studies found significant impairments in TLE compared to HC on tests of memory and executive function.

In 26 of the TLE studies, the samples were divided by laterality of seizure focus with the primary pathology affecting the right temporal lobe (RTL $n = 846$) or the left temporal lobe (LTL $n = 1,068$). In pre-surgical TLE, the direct comparison of LTL and RTL groups indicated that the LTL group showed impaired verbal memory and the RTL group, less consistently, impaired visuospatial memory.

The most common impairment observed in TLE related to surgery was in verbal memory. This finding was also associated with laterality, 24 studies reporting decline in verbal memory from pre- to post-surgery in LTL patients, whereas in RTL there was a less consistent decline in visuospatial memory. No significant differences in attention were found for laterality or pre- to post-surgery in TLE.

Table 3 shows the results of individual neuropsychological tests that were reported in more than one study, for BD-I and TLE. Of note, the total number of neuropsychological tests used across all studies differed between BD-I (27) and TLE (11); this was not evenly distributed across cognitive domains. The number of studies where any executive function instrument was administered in TLE was only 4 (2 WCST, 2 COWAT) of 29 compared to 21 of 27 in BD-I. One study compared RTL, LTL and HC and showed that all patients were impaired on the WCST relative to HC (87). The number of studies where any verbal memory instrument was administered was 26 of 29 in TLE compared to 14 of 27 in BD-I. The comparable figures for visuospatial memory instruments were 25 of 29 in TLE and 11 of 27 in BD-I. Similarly, only 6 studies measured attention in TLE compared to 17 studies in BD-I. Thus, while both fields have seen sustained research activity in identifying neuropsychological deficits, the focus of inquiry in TLE has been on verbal and visuospatial memory and in BD-I executive function.

Notwithstanding the differences in the intensity and focus of neuropsychological testing in both conditions, consistent results emerging from this study emphasize deficits in verbal memory, which have been reported in the majority of studies that have examined this area in both BD-I and TLE.

TABLE 1 | Summary of included studies on euthymic bipolar disorder.

Reference	*n*	Medications bipolar sample	Neuropsychological test parameters	Results
Altshuler et al. (37)	BD 40 SZ 20 HC 22	Li 25, AC 12, AD 4, AP 6, BZD 3	WAIS-R block design, vocab; TMT, WCST, Stroop; VFT; CVLT; ROCFT; Star mirror tracing Task, PR	BD impaired verbal memory and executive functioning
Bas et al. (38)	BD 60 HC 41	Li 39, AP 37, LTG 9, VPA 21	Stroop, TMT A and B; WMS-R visual reproduction; RAVLT	BD impaired on RAVLT
Bora et al. (39)	BD 514 BD-II 42 HC 416	Li 63.2%, VPA 47.6%, AP 47.2%, AD 5.7%	Stroop. WCST	Deficits exist in subgroups who have severe and global cognitive deficits
Chang et al. (40)	BD 23 BD-II 23 HC 23	BD Li 13, AP 15, LTG 7, VPA 9	WAIS-R block design and vocab; CVLT, VFT	All NS
Chou et al. (41)	BD 23 HC 33	AP 13, VPA 19	The Color Trails Test, WCST; WMS-III – Word Lists Test, Face Test; Go/No-GO, Test for Attentional Performance	BD impaired faces memory and WCST
Deckersbach et al. (42)	BD 25 HC 25	Li 11, AC 9, AD 9, AP 3	ROCFT	Immediate recall BD impaired, copy and recognition preserved
Deckersbach et al. (11)	BD 30 Obsessive compulsive disorder 30 HC 30	Li 13, AC 11, AD 8, AP 4	CVLT	CVLT BD impaired learning and delayed free recall
Dell'Osso et al. (43)	BD 15 BD-II 13 HC 27	BD Mono 2, Poly 12	N-Back	NS HC and BD
Dittmann et al. (44)	BD 65 BD-II 38 HC 62	BD Li 27, AD 10, AP 33, CBZ 4, VPA 28	TMT; HAWIE-R; WAIS-III letter number sequencing; RBANS	Psychomotor speed, working and delayed memory, verbal learning, executive functioning BD impaired
Dixon et al. (45)	BD manic 15 dep 15, eu 15, HC 30	Eu Li 15, AD 8, AP 10, AC 2	WAIS-R Vocab; Stroop; FAS; Hayling sentence completion test; Cognitive Estimates Test	VF total responses, Hayling response initiation latency, error score and using strategy, stroop EuBD impaired
Doganavşargil-Baysal et al. (46)	BD 60 HC 20	Li 11, MS + AP 12, 2MS 12, VPA 6	WCST, TMT, Stroop; RAVLT; Cancelation test	Significant differences on all measures between BD and HC
Doganavşargil-Baysal et al. (46)	BD 54 HC 18	Li 10, MS + AP 27, 2MS 11, VPA 5	WCST; RAVLT	Both measures BD < HC
Doruk et al. (47)	Manic 20 Dep 10 Eu 21	Unknown	Stroop; Serial Digit Learning Test; RAVLT; Cancelation Test	NS HC and EuBD
Fistikci et al. (48)	BD 25 HC 25	Li 25	WCST; Montreal Cognitive Assessment	NS HC and BD
Frangou et al. (49)	BD 10 Un offspring 15 HC 43	Li 5, AC 3	WCST; Hayling sentence completion	WCST BD and offspring made more errors
Hsiao et al. (50)	BD 30 BD-II 37 HC 22	VPA 29	WAIS-III digit symbol; TMT; WMS-III	Verbal memory, working memory, psychomotor speed, executive function BD impaired
Martino et al. (51)	BD 48 BD-II 37 HC 34	AD 16, AP 28, BZD 23, MS 48	WAIS vocab, digit span; TMT, WCST, IGT; Memory battery of Signoret	Verbal memory, attention and executive functions impaired
Muralidharan et al. (52)	BD 72 HC 40	AP 27, Li 34, VPA 38	TMT, Stroop; CANTAB; CVLT; WMS-III LNS	P on VPA more working memory deficits than Li or HC
Muralidharan et al. (53)	BD 68 HC 38	AP 51, Li 32, MS + AP 50, VPA 32	TMT, Stroop; CANTAB; CVLT; WMS-III letter number sequencing	Verbal and visuospatial memory, working memory and executive function BD impaired.
Normala et al. (54)	BD 40 HC 40	AP 6, MS 11, MS + AD 1, MS + AP 22	WAIS Digit span; TMT; Verbal Fluency	Executive and attention functioning BD impaired

(Continued)

TABLE 1 | Continued

Reference	n	Medications bipolar sample	Neuropsychological test parameters	Results
Pattanayak et al. (55)	BD 30 HC 20	AP 5, LTG 2, Li 21, VPA 11	VIQ; TMT, Stroop; N-Back; Postgraduate Institute Memory Scale	Attention, information processing speed, executive function, verbal memory BD impaired
Radwan (56)	BD 30 HC 30	Unknown	WAIS; WCST; WMS; CPT	All BD impaired
Sepede et al. (57)	BD 24 Unaffected rels 33 HC 24	AD 10, AP 15, BZD 8, Li 3, MS 9	CPT	Sustained attention impaired BD and rels
Trivedi et al. (58)	BD 15 HC 15	CBZ 1, Li 8, VPA 6	WCST; SWMT; CPT	Executive function BD impaired
Trivedi et al. (59)	BD 15 SZ 15, HC 15	Unknown	WCST; SWMT; CPT	Executive function BD impaired
Yates et al. (60)	BD dep 34 BDEu 31, HC 34	AD 9, AP 18, BZD 9, MS 29	WAIS-III	Verbal measure BD impaired
Zubieta et al. (61)	BD 15 HC 15	AP 3, CBZ 2, Li 7, VPA 12	WAIS-R: digit span; WCST, Stroop; WMS-R; verbal fluency; test of variable attention	Verbal learning, executive function, motor coordination and sequential memory BD impaired. NS verbal fluency or attention

BD, bipolar; BD-II, bipolar II; HC, healthy controls; SZ, Schizophrenia; Li, lithium; AC, anticonvulsant; AD, antidepressant; AP, antipsychotics; BZD, benzodiazepine; CBZ, carbamazepine; LTG, lamotrigine; MS, mood stabilizer; VPA, valproate; Mono, monotherapy; Poly, polytherapy; AMIPB, Adult Memory and Information Processing Battery; BVRT, Benton Visual Retention Test; VLMT, Verbaler Lern- und Merkfähigkeitstest; DCS-R, Diagnosticum für Cerebralschädigung – II; NAART, North American Adult Reading Test; WRAT, Wide Range Achievement Test; WAIS, Wechsler Adult Intelligence Scale; CPT, Continuous Performance Test; CVLT, California Verbal Learning Test; RAVLT, Rey Auditory Verbal Learning Test; WCST, Wisconsin Card Sorting Test.

DISCUSSION

To our knowledge, this is the first systematic review directly comparing the literature on cognitive function in BD-I and TLE. Consistent with the meta-analyses of cognition in euthymic BD-I, our review showed impairments on a wide range of cognitive measures. In the individual studies reviewed, the most commonly reported impairments in BD-I were in executive function, attention span, and verbal memory. The impairments of executive function in patients with BD-I may be suggestive of an underlying dysfunction in the prefrontal cortex (3).

In TLE studies, a decline in pre- to post-surgery in verbal memory was commonly reported in patients with seizures originating from the LTL, and less consistently, in visuospatial memory in patients with RTL epilepsy. Functional MRI studies have revealed that the right hemisphere is associated with spatial memory (91). In our sample, executive function was not widely examined in patients with epilepsy; however, an impairment was found. For executive function, two instruments were employed across four studies, three of which showed a difference between pre- to post-surgery scores and one study found impaired performance in TLE relative to HC participants.

In keeping with our results, meta-analyses of memory function pre- to post-surgery reported that, following a resection of the LTL, a clear decline in verbal memory is observed, an effect that is particularly salient for immediate verbal recall. However, the pattern of impairment following partial resection of the RTL showed a trend for improvement on tasks of non-verbal memory (92). This suggests that memory impairments are state markers affected by seizures and abnormalities in the temporal lobes. Other factors that affect cognitive performance in TLE are the chronicity of the condition, older age, lower intellect, and greater abnormalities shown on imaging (92). Another meta-analysis found that the evidence regarding post-surgery outcome on visuospatial memory following right anterior temporal lobectomy was less clear (93).

In TLE, it is unclear whether frontal lobe impairments shown on executive function measures are a product of temporal lobe involvement or are a side effect of the propagation of epileptic activity from the epileptic zone (94). Other evidence has suggested that the prefrontal cortex, in particular the orbitofrontal cortex, is influenced by ictal discharges from the mesial temporal lobe (95). Some studies have shown that the temporal neocortex is implicated in executive function implying that a frontotemporal network is used for processing information (96).

This review emphasizes that prior research on cognitive impairments in the fields of BD-I and TLE has employed methodologies that reflect different research questions. The BD-I literature predominantly examines cognition as a characteristic of the disorder itself, on a par with symptoms and potentially amenable to therapeutic intervention. The TLE literature is concerned with the effects of ablative surgery that aims to remove seizure foci but may consequently also directly affect healthy brain tracts. It addresses whether cognitive function improves or declines subsequent to surgery and the moderating effects of laterality.

The majority of BD-I studies compare euthymic patients with HC, whereas in the epilepsy studies, patients act as their own controls in relation to surgical intervention and laterality. In addition, given that the BD-I studies are interested in trait markers in the euthymic phase, they routinely report the quantitative differences between patients and HC, rendering the results suitable for incorporation in meta-analytic studies. The TLE literature has focused

TABLE 2 | Summary of included studies on pre-surgical temporal lobe epilepsy (TLE).

Reference	n	Neuropsychological test parameters	Results
Baxendale and Thompson (62)	Right temporal lobe (RTL) 133 LTL 157	WAIS PIQ, VIQ; AMIPB	Verbal memory decline post-surg left temporal lobe (LTL)
Baxendale et al. (63)	RTL 146 LTL 177	WAIS PIQ, VIQ; AMIPB; Birt Memory and Information Processing Battery	RTL and LTL at equal risk of post-surg decline
Berenbaum et al. (64)	LTL 57	WAIS Digit Span; CVLT	CVLT decline post-surg
Bjørnaes et al. (65)	RTL 50 LTL 41	WAIS Digit Span; Benton Visual Retention Test (BVRT); Design Learning and Retention Test; Verbal List Learning and Retention; Tactual Performance Test	Improvement at 2-year follow up post-surg
Chelune et al. (66)	RTL 19 LTL 23	WAIS-R VIQ, PIQ; WMS-R; RAVLT; COWAT, Halstead-Wepman Aphasia Screening Exam, BNT, Speech Sounds Perception Test; Hooper Visual Organization Test, Seashore Rhythm Test	LTL decline post-surg
Chiaravalloti et al. (67)	RTL 16 LTL 10	WMS-III Faces Subtest; Graduate Hospital Facial Memory Test	RTL < LTL both pre- and post-surg
Chiaravalloti (68)	RTL 42 LTL 28	CVLT; Graduate Hospital Facial Memory Test	Verbal memory post-surg decline LTL, RTL improved. Visuospatial memory post-surg decline RTL, LTL improvement
Fernandes et al. (69)	RTL 23 LTL 24 healthy controls (HC) 28	WAIS-R Block design, Vocabulary; WMS-R; RAVLT	Cognitive scores post-surg decline low pre-surg scores. Non-verbal memory post-surg RTL decline, verbal and visuospatial memory LTL decline
Giovagnoli et al. (70)	RTL 12 LTL 12 HC 36	Raven's Colored Progressive Matrices; Attentive Matrices; Verbal Selective Reminding Procedure, Story Recall, Verbal Memory Distractor Test; Visual Selective Reminding Procedure, ROCFT, Visual Memory Distractor Test	Verbal memory pre- and post-surgery LTL impaired relative to HC. Visual deficits present in both groups relative to HC
Gleissner et al. (71)	RTL 63 LTL 52	VLMT; DCR-S	Verbal memory LTL decline
Glosser et al. (72)	RTL 13 LTL 8 HC 10	Boston Naming Test; CVLT Benton Facial Recognition, Graduate Hospital Facial Memory	Recognition of familiar faces and learning new faces RTL impaired. Names of familiar faces LTL impaired
Helmstaedter et al. (73)	LTL 47	Verbal Learning and Memory Test; RAVLT	Delayed recall and recognition post-surg improvement
Hermann and Wyler (74)	RTL 14 LTL 15	COWAT; Token Test	Language tests pre-surg LTL deficit
Hermann et al. (75)	RTL 31 LTL 26	CVLT	Verbal memory post-surg RTL increased
Hermann et al. (76)	RTL 26 LTL 36	WAIS-R Digit Span; Multilingual Aphasia Examination Visual Naming Test; CVLT	CVLT post-surg decline LTL
Köylü et al. (77)	RTL 12 LTL 14	List learning task	LTL post-surg decline
Lee et al. (78)	LTL 38	RAVLT; ROCFT	Memory post-surg decline
Loring et al. (79)	RTL 13 LTL 16	Selective Reminding Test, Serial Digit Learning, ROCFT, Form Sequence Learning	Complex figure RTL impaired. Verbal memory decline LTL
Malikova et al. (80)	RTL 11 LTL 26	WAIS-R; WMS-R; Verbal Fluency Test	FSIQ, global and verbal memory, attention, and working memory all improved post-surg
Morino et al. (81)	RTL 31 LTL 31	WMS-R; Miyake Verbal Retention Test; BVRT	Memory RTL improved post-surg. Verbal memory LTL post-surg improved
Quigg et al. (82)	RTL 16 LTL 14	TMT; BNT; CVLT; WMS-R Logical Memory Scale	BNT and CVLT LTL decreased post-surgery. Language and verbal memory LTL increased. TMT increased
Seidenberg et al. (83)	RTL 30 LTL 46	CVLT	Free recall LTL decline post-surgery

(Continued)

TABLE 2 | Continued

Reference	n	Neuropsychological test parameters	Results
Selwa et al. (84)	RTL 14 LTL 17 Non-surgical TLE 28	WAIS-R; WMS	FSIQ, Logical Memory RTL improved post-surg. Verbal memory decline LTL post-surg
Shamim et al. (85)	RTL 14 LTL 16	WAIS-III; WMS-III	Verbal memory deficit post-surg LTL
Stretton et al. (86)	RTL 17 LTL 16 HC 15	WAIS-III Digit Span; Gesture Span Task; Motor Sequences Task; Dot-Back Paradigm	Working memory pre-surg RTL and LTL worse than HC. WM improved post-surg LTL
Tisser et al. (87)	RTL 10 LTL 15 HC 22	WAIS-R; WCST	WCST RTL and LTL impaired, improved post-surg
Trenerry and Jack (88)	RTL 34 LTL 34	WAIS-R; WCST	The WCST is not useful for lateralizing seizure onset in TLE
Trenerry et al. (89)	RTL 36 LTL 44	WAIS-R; WMS-R; RAVLT; Visual Spatial Learning Test	Verbal and visual memory LTL improved post-surg
von Rhein et al. (90)	RTL 20 LTL 32	VLMT; DCS-R; BNT; Token Test	Verbal Memory impaired post-surgery. Naming decline post-surgery LTL

Tests of executive function: WCST, FAS, TMT-B, Stroop, Hayling Sentence Completion Test, CANTAB: Intra Extra Dimensional Set Shifting, CANTAB: Stockings Problem; Tests of Verbal Memory—CVLT, RAVLT, WAIS Vocab, WMS-R: Logical Memory, WMS-R: Verbal Paired Associates, Token Test, VLMT: Verbaler Lern- und Merkfähigkeitstest; Tests of non-verbal memory- ROCFT, WMS: Visual reproduction, WMS-R: Design Memory, WMS-R Visual Reproduction, WMS-III: Face Test, CANTAB: Spatial recognition memory, CANTAB: Pattern Recognition Memory, CANTAB: Paired Associates Learning; Attention span WAIS: Digit Span, Adult Memory and Information Processing Battery (AMIPB); sustained attention CPT; working memory SWMT, N-Back, WAIS: Letter Number Sequencing, WMS-III: Letter Number Sequencing, CANTAB: Spatial Working Memory.

TABLE 3 | Neuropsychological test findings summary table (for tests used more than once) in studies of bipolar disorder (BD) and temporal lobe epilepsy (TLE).

Measure	BD		TLE		Pre- to post-surgical		Laterality effects
	Use in studies, number of participants BD	BD < HC sig	Use in studies, number of participants TLE	sig	↑	↓	
Executive function							
WCST	12 studies BD n = 859, healthy controls (HC) n = 676	11	2 studies Right temporal lobe (RTL) n = 44, left temporal lobe (LTL) n = 49, HC n = 22	1	↑1		
COWAT(FAS)	5 studies BD n = 133, HC n = 130	2	2 studies RTL n = 33, LTL n = 38	2	↑1		Higher score LTL group pre- assoc. with greater impairment post-surg
TMT-B	9 studies BD n = 513, HC = 339	7					
Stroop	10 studies BD n = 895, HC = 642	7					
Hayling Sentence Completion Test	2 studies BD n = 25, HC n = 73	2					
CANTAB: Intra Extra Dimensional Set Shifting	2 studies BD n = 140, HC n = 78	2					
CANTAB: Stockings Problem	2 studies BD n = 140, HC n = 78	2					
Verbal memory							
CVLT	5 studies BD n = 233, HC n = 153	3	7 studies RTL n = 158, LTL n = 215, HC n = 10	6		↓6	Post-surg LTL decline 6 RTL > LTL 1

(Continued)

TABLE 3 | Continued

Measure	BD		BD < HC sig	TLE	sig	Pre- to post-surgical ↑ ↓		Laterality effects
	Use in studies, number of participants BD			Use in studies, number of participants TLE		↑	↓	
RAVLT	3 studies BD n = 141, HC = 79		2	5 studies RTL n = 78, LTL n = 176, HC n = 28	5		↓5	Post-surg LTL decline 5
Verbal comprehension: WAIS Vocab	4 studies BD n = 187, HC n = 173		0					
WMS-R: Logical Memory				6 studies RTL n = 206, LTL n = 256, HC n = 28	4	↑3	↓1	LTL < RTL 1
WMS-R: Verbal Paired Associates				4 studies RTL n = 119, LTL n = 151, HC n = 28	4	↑2	↓1	LTL < RTL 1
Token Test				2 studies RTL n = 34, LTL n = 47	1	↑1		Post-surg LTL improved 1
VLMT: Verbaler Lern- und Merkfähigkeitstest				2 studies RTL n = 83, LTL n = 82	2		↓2	
Visuospatial memory								
ROCFT	2 studies BD n = 65, HC = 47		0	3 studies RTL n = 25, LTL n = 62, HC n = 36	2	↑1		LTL < RTL 1
WMS: Visual reproduction	3 studies BD n = 105, HC n = 78		0	2 studies RTL n = 27, LTL n = 29	0			
CANTAB: Spatial recognition memory	2 studies BD n = 140, HC n = 78		2					
CANTAB: Pattern Recognition Memory	2 studies BD n = 140, HC n = 78		2					
CANTAB: Paired Associates Learning	2 studies BD n = 140, HC n = 78		2					
WMS-R: Design Memory				4 studies RTL n = 78, LTL n = 93, HC n = 28	2	↑1	↓1	RTL decline 1
WMS-R Visual Reproduction				5 studies RTL n = 241, LTL n = 484, HC n = 28	2	↑1	↓1	RTL decline 1
WMS-III: Face Test				1 study RTL n = 16, LTL n = 10	1		↓1	RTL decline 1
Graduate Hospital Facial Memory				3 studies RTL n = 71, LTL n = 46, HC n = 10	3	↑1		RTL < LTL 2
Benton Visual Retention				2 studies RTL n = 31, LTL n = 72	0			
Diagnosticum für Cerebralschädigung				3 studies RTL n = 83, LTL n = 253	2		↓1	
Spatial ability								
WAIS: Block design	4 studies BD n = 124, HC n = 109		0					
Attention span								
WAIS: Digit Span	3 studies BD n = 103, HC n = 89		2	4 studies RTL n = 93, LTL n = 150, HC n = 15	0			
TMT-A (also processing speed)	10 studies BD n = 513, HC n = 339		8					
WAIS: Digit Symbol (also processing speed)	3 studies BD n = 91, HC n = 86		3					
CANTAB: Rapid Visual Information	2 studies BD n = 140, HC n = 78		2					

(Continued)

TABLE 3 | Continued

Measure	BD			TLE		Pre- to post-surgical		Laterality effects
	Use in studies, number of participants BD	BD < HC sig		Use in studies, number of participants TLE	sig	↑	↓	
Adult Memory and Information Processing Battery (AMIPB)				2 studies RTL *n* = 279, LTL *n* = 334	2	↑1	↓1	
Sustained attention								
CPT	4 studies BD *n* = 84, HC *n* = 84	2						
Working memory								
SWMT	2 studies BD *n* = 30, HC *n* = 30	0						
N-Back	2 studies BD *n* = 45, HC *n* = 47	0						
WAIS: Letter Number Sequencing	3 studies BD *n* = 126, HC *n* = 126	3						
WMS-III: Letter Number Sequencing	2 studies BD *n* = 140, HC *n* = 78	3						
CANTAB: Spatial Working Memory	2 studies BD *n* = 140, HC *n* = 78	2						

↑ refers to an increase, ↓ a decrease from pre- to post-surgery, sig refers to the number of studies with a significant result, laterality comments only significant main effects or interactions are discussed.

on statistically significant differences pre- to post-surgery and has not reported information in a form suitable for meta-analysis of pre-surgical cognitive functioning. Therefore, we have employed a systematic review methodology to examine and compare the profile of cognitive deficits in the two conditions. As indicated in the Section "Results," the focus of inquiry of the neuropsychological tests employed in the BD-I studies is predominantly on frontal lobe functions and in TLE on verbal and visuospatial memory.

There are significant differences in the experimental designs examining cognition in the two patient groups. In BD-I studies, cognition is tested broadly with a wide range of measures, with a HC comparison group and statistical control for medication use. This allows for observed deficits to be interpreted as trait markers of BD-I. This is further supported by familial studies that show similar patterns of impairments among family members and patients (89). By contrast, studies assessing cognitive performance in pre-surgical patients with epilepsy do so generally without HC. Only five studies included HC (*n* = 111), consequently the findings have limited depth compared to those in the BD-I literature (*n* = 1,142). The pre-surgical neuropsychological workup consists mostly of tests of memory function, which is not surprising given that the surgery involves removing parts of or the whole temporal lobe.

In general, the studies on BD-I report the types of medications taken by patients at the time of testing (as shown in **Table 1**), which may have impacted the results. By contrast, in the epilepsy samples, it was typically not reported whether patients were receiving medication at the time of testing. A study that examined the effects of atypical antipsychotics on cognition in euthymic BD-I patients found that untreated patients showed better performance than those taking medication (93). Many patients with BD-I are

treated with anticonvulsants that may worsen or enhance cognition (97). Of the total sample of 884 patients with BD-I included in the systematic review, 299 were taking lithium at the time of testing. A review of the effects of lithium on cognition found that impairments on tasks of psychomotor speed and verbal memory were present, whereas no effect was found on visuospatial ability or attention (97). Thus, cognitive performance may be impaired in various ways by different medications. A recent randomized crossover study examined the effects of methylene blue on cognition and mood-related symptoms in euthymic BD-I and BD-II. Neither low (15 mg) control doses nor high active doses (195 mg) had a significant effect on cognition (98). In rats, methylene blue prevents methylmalonate-induced seizures and oxidative damage in the striatum (99) providing interesting leads for future research into the overlaps between BD and epilepsy.

While this paper has provided an overview of the literature, it is subject to a number of limitations. One such factor is the differences of experimental designs in BD-I and TLE, which meant that a head-to-head meta-analytic comparison was not feasible. As discussed previously, the effect of medication was not uniformly controlled in BD-I and was either not reported or not systematically recorded in the epilepsy samples. In order to determine whether cognitive deficits are related to the illness and not undesirable side effect of medication, examination of otherwise stable drug-free patients would be of interest. The period of time between episodes (mania, depression, or seizures), time of testing, hospitalizations, and the presence of psychotic features were not considered in this review. In BD-I patients, the presence of sub-clinical symptoms is common, even in those patients who are rated as euthymic at the time of testing and may have impacted performance overall (3).

Although there is wide variation in the diagnostic criteria of euthymia, our study aimed to control for this by using the HAMD and YMRS as cutoffs; however, longitudinal measurements would have been advantageous to characterize proximity to manic or depressive episodes. Residual mood symptoms are also an important consideration in epilepsy where depression is the most common psychiatric comorbidity (18). In community-based samples, the rates of depression in epilepsy range from 20 to 30% and in hospital samples 20–55% (100, 101). It has been established that depression can cause cognitive impairments, particularly in the domains of attention, psychomotor activity, and memory all of which were relevant to this review (102).

We suggest a strong case may be made for a study comparing neuropsychological tests to assess deficits in BD-I, TLE, and matched HC. In future research, a comprehensive test battery employing tests of attention, executive function, memory, and psychomotor speed, coupled with imaging techniques, should be employed in both disorders relative to HC. This would provide valuable information on the effects of both BD-I and TLE on temporal and other cerebral areas as well as the effects of medication on neuropsychological test parameters. This would also be of value in identifying putative temporal lobe involvement in BD-I.

AUTHOR CONTRIBUTIONS

EB, KK, MG, and BT contributed to the design of the project, the analysis and discussion of the results and write up of the paper with KK, MG, and BT contributing their specialist perspective. EB and KK assessed the suitability of papers for inclusion in the manuscript and contributed to the PRISMA review.

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