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COGNITIVE SCREENING TESTS FOR PATIENTS WITH EPILEPSY: A SYSTEMATIC REVIEW FOCUSING ON TEST VALIDITY AND DIAGNOSTIC ACCURACY

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Abstract. Epilepsy often affects cognition. The aim of this review was to systematically examine evidence for the validity of cognitive screening tests currently being used in epilepsy. MEDLINE and EMBASE databases were searched from 1946/1947 until the 12th of March 2019. Only studies that met the eligibility criteria and which reported at least some diagnostic accuracy data were included. Seven studies met the inclusion criteria, relating to five screening tools. The EpiTrack was the most commonly used tool, while the test most frequently used as a reference standard was the Digit Span. Diagnostic accuracy of cognitive screening tools in epilepsy remains limited and the risk of bias is generally high. EpiTrack is proposed as the appropriate screening tool to begin the assessment with, as it is specifically constructed for and validated on patients with epilepsy, provides specific cutoff points, and has satisfactory reliability.

Key words: Cognitive screening tools, Digit span, Epilepsy, EpiTrack

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INTRODUCTION

Epilepsy is defined as: "(1) at least two unprovoked (or reflex) seizures occurring > 24 h apart; (2) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years from the initial seizure; (3) diagnosis of an epilepsy syndrome (Fisher et al., 2014). It can be the result of several underlying causes (de Groot et al., 2012; Hauser & Hesdorffer, 1990; Staley et al., 2011) and is among the 25 most common conditions leading patients to spend years living with a disability (Vos et al., 2012). Epilepsy has a great impact in many domains of patients' lives (Jones-Gotman et al., 2010) and affects cognition because of various reasons: the epileptiform activity, which is produced by the condition itself, underlying pathologies that cause the epilepsy, medication side effects, potential cumulative head injuries from unexpected collapse, and in some cases consequences of surgery (Gavrilovic et al., 2019; Kwan & Brodie, 2001; Meschede et al., 2018; Staley et al., 2011; Witt et al., 2018; Zhang et al., 2018).

More specifically, it has been found that epileptiform discharges predicted cognitive ability in general and memory function in sixty-nine patients with genetic generalised epilepsy (Loughman et al., 2016). Patients with temporal lobe epilepsy show impairments either in multiple cognitive domains, or specifically in attention and executive functions, frontal lobe functions, memory, or language (Allone et al., 2017; Noebels, 2011; Uslu et al., 2019). Furthermore, according to Lin et al. (2012), various types of anti-epileptic medication have negative effect on motor or cognitive speed, mood, and memory. Finally, research in children with epilepsy has detected impaired intelligence scores, executive functions, visual attention, and spatial ability (Cheng et al., 2017; Lin et al., 2012). Indeed, in the review of MacAllister and Schaffer (2007), impairments in global cognitive functioning, visual spatial function, visual and verbal memory, attention, executive functioning, and language abilities, were found in children with different epilepsy types, including generalized idiopathic epilepsies— e.g., childhood and juvenile absence epilepsy— or focal epilepsies such as temporal lobe epilepsy, frontal lobe epilepsy, the Lennox–Gastaut Syndrome, and West Syndrome.

It is therefore pivotal to examine patients' cognitive abilities in order to investigate possible cognitive changes as a result of epileptiform activity, medication prescribed, or surgical impact. However, administering a comprehensive neuropsychological battery on a frequent basis is not always feasible, as is time-consuming and cost-intensive; a screening test that can be administered quickly and reliably to give an impression of cognitive change is therefore desirable in busy clinical settings (Wilson et al., 2015).

There are several tools that have been used in the past to screen for impairment in persons with epilepsy, either in clinical practice or in research (Huang et al., 2005;

Natham et al., 2018; Witt et al., 2015). Among the tools used, were the Cognitive Ability Screening Instrument (CASI; Teng et al., 1996), the Mini-Mental State Examination (MMSE) (Folstein et al., 1975) and the Montreal Cognitive Assessment (MOCA; Nasreddine et al., 2005). Specifically, researchers sought to examine cognitive impairment in specific types of epilepsy (Phabphal & Kanjanasatien, 2011), to assess the consequences of surgery (Zhang et al., 2018), the impact of anti-epileptic medication on cognition (Liguori et al., 2018), to investigate the association of cognitive impairment with other factors (Palanisamy et al., 2016).

However, none of these studies looked at diagnostic accuracy in terms of the ability of these screening tools to identify cognitive impairment in epilepsy based on a cutoff score. Additionally, no review has been carried out regarding the most appropriate/sensitive cognitive screening test that can be used specifically to screen this population. Research in this domain could help clinicians select the best tool to utilise in order to assess patients briefly, detect possible impairment and suggest whether a patient would benefit from a comprehensive neuropsychological assessment. The aim of this review was to systematically examine the existing literature regarding cognitive screening tests used in epilepsy patients, focusing on evidence on their validity. This will contribute to the discussion about the accuracy of standardized cognitive screening tests used to detect cognitive impairment in epilepsy patients.

METHOD

Design

The target condition was epilepsy, as defined by the International League Against Epilepsy (Fisher et al., 2014), with the population of interest being people with epilepsy. The index tests were the cognitive screening tests used, whereas reference standards were the measures used to quantify reliability and/or validity of the index test.

Eligibility

The studies to be included in this review had to fulfill the following eligibility criteria:

- a) Firstly, they were validation studies (meaning that the goal of the study was to investigate if the tool was able to distinguish between patients with and without cognitive impairment based on either diagnostic accuracy statistics, or statistical significance between groups;
- b) they were empirical studies presenting original results (i.e., the results should not constitute part of a review);
- c) the results were compared to another reference standard (as there are no specific cognitive tests that diagnose cognitive impairment in epilepsy, there were no limitations regarding the reference standards being used);
- d) the full article should be available (not just the abstracts or conference proceedings);
- e) the language in which the papers were published should be English.

Search strategy

For this review, MEDLINE [Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) 1946 to date] and EMBASE (Embase 1947-Present, updated daily) were searched. The keywords and subject headings used are shown in Table 1. The search included only studies published in English and the dates were set as beginning from 1946 and 1947 respectively to the 12th of March 2019.

Table 1. Keywords and MeSH terms of search strategy used in MEDLINE and EMBASE databases study selection

1.	Epilepsy, Absence/ or Epilepsy, Rolandic/ or Epilepsy, Post-Traumatic/ or Epilepsy, Benign Neonatal/ or Epilepsy, Generalized/ or Epilepsy, Frontal Lobe/ or Epilepsy, Tonic-Clonic/ or Epilepsy, Partial, Motor/ or Epilepsy, Complex Partial/ or Epilepsy, Temporal Lobe/ or exp Epilepsy/ or Drug Resistant Epilepsy/ or Epilepsy, Reflex/ or Epilepsy, Partial, Sensory/ or Myoclonic Epilepsy, Juvenile/
2.	epilep*.tw. orepilep*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
3.	seizure*.tw.
4.	1 or 2 or 3
5.	cognit* screen*.tw. orcogn* screen*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
6.	("brief cognit* test" or "brief cognit* assessment" or "screening tool").mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
7.	5 or 6
8.	4 and 7

Study selection

After the appropriate terms were inserted in the database, the process of study selection started. First, all duplicates were removed. Next, all titles and abstracts were screened. After the studies considered to match the review question were identified from title and/or abstract, the full-text articles were read to determine which articles fully met the eligibility criteria and could be included in the review.

The flow chart of this study is presented according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards (Moher et al., 2009) in Figure 1.

Cognitive screening tests in epilepsy

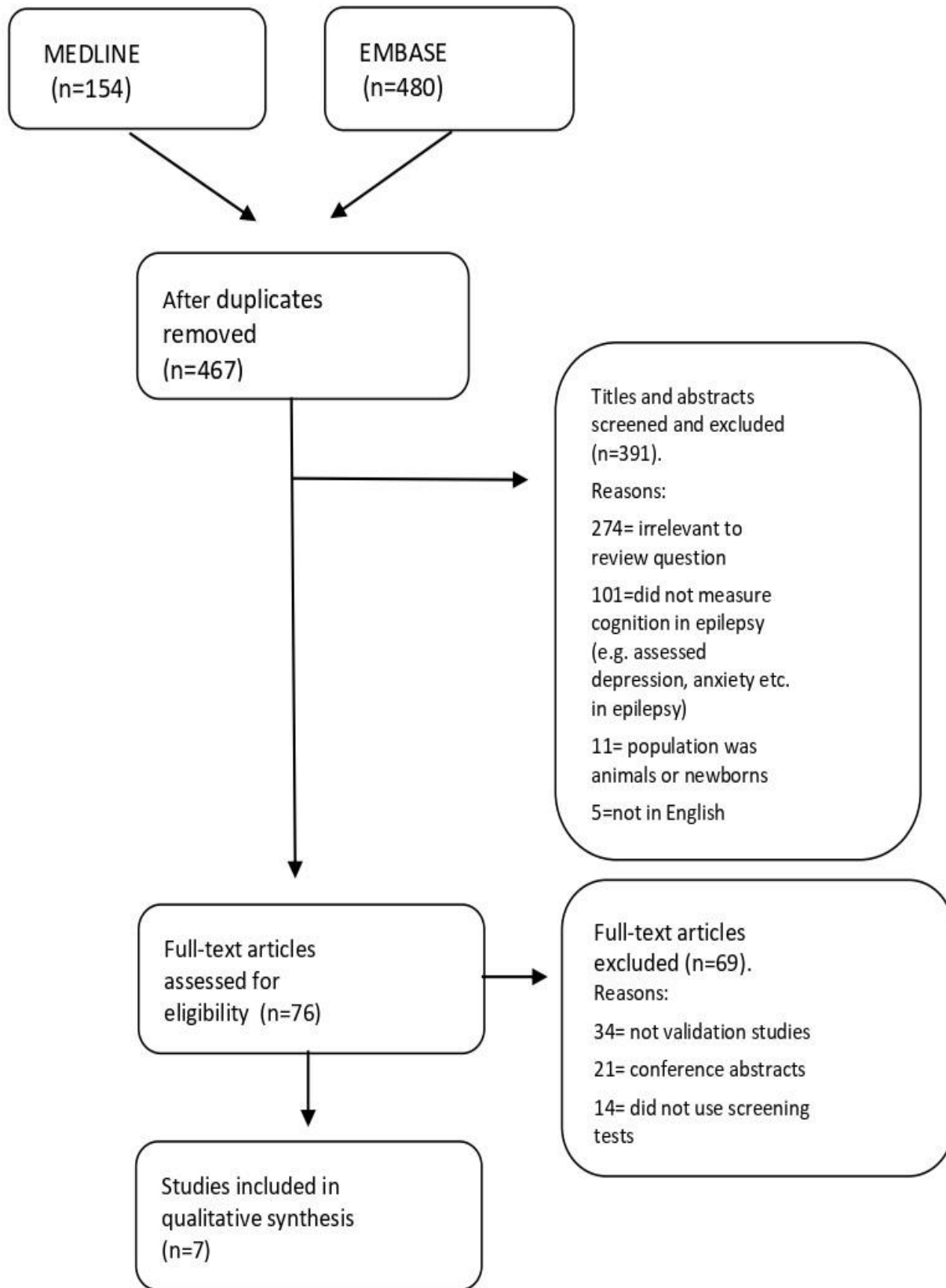


Figure 1. Flow diagram describing search strategy and results

Data extraction

Key study information was recorded in a data extraction form that included: sample size; place of examination (e.g., day care centre); tests given; reference standards used; time intervals. In a separate table, descriptive details of the studies were summarized, detailing the sample size and demographic characteristics as well as which of the diagnostic accuracy features (reliability, validity, sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV), cutoffs) were reported in each of the studies.

Quality assessment

To assess the quality of the studies, Version 2 of the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) (Whiting et al., 2011) was used. This tool assesses four domains; specifically, it examines the participants, index test, reference standard and flow and timing of the studies. In each of the four domains, the rater had to assess two factors, namely, risk of bias and applicability of the study. This means that the rater decided, for example, if the selection of participants, the tools administered, etc., could potentially be considered as biased, and also if there were aspects of the study which may render it inappropriate to the review question. In order for the author to decide, there were signaling questions in each domain and after careful consideration the user marked the signaling questions on a scale with three choices (low/high/unclear). After the two signaling questions in the risk of bias section and the one signaling question in the applicability section were marked, the first author of the study gave a total mark for risk of bias and for applicability in each of the four domains.

Synthesis

The findings of the studies were summarised in tables. Descriptions of the screening tools included in the review, such as details of the subtests they consisted of, the functions they assessed and the form of test administration (i.e., paper and pencil or computerised) were also provided. Meta-analysis was not possible due to heterogeneity of reference standards that were used, different cutoffs, sample sizes and characteristics.

RESULTS

Search results

A total of 634 records were initially identified. After duplicates were excluded, 467 records were screened. Based on titles and abstracts, 391 records were excluded, leaving

76 for full text review. After careful reading of full texts seven studies met the eligibility criteria and were included in the review. The detailed process and reasons for exclusion of studies are presented in Figure 1.

Description of studies

The seven studies which were included in this review (Gao et al., 2014; Helmstaedter et al., 2010; Hoppe et al., 2009; Kadish et al., 2013; Kurzbuch et al., 2013; Lutz & Helmstaedter, 2005; Walterfang et al., 2011) were published in English between 2005 and 2014.

The sample sizes for healthy controls ranged in five studies from 83 to 277 persons whereas two of the studies did not recruit healthy people; one study compared the epilepsy group against dementia and neurological disorders group and the other study compared patients' data with healthy controls' mean scores acquired from a previous validation study. As far as clinical samples are concerned, the number of participants ranged in the seven studies from 22 to 240, with age between 6 and 74 years. In terms of education level, there were people with no specific qualification, as well as participants who had obtained various years of formal education. All studies included both males and females. Participants of two studies were children. In Table 2 sample sizes and demographic characteristics are given in detail.

Reporting on source of recruitment varied. With regards to healthy controls, four out of the five studies that included healthy participants did not state where those participants were recruited from. Only one of the five studies that recruited healthy controls reported on the source of the sample (students from three different representative schools in Germany). Clinical participants in the seven studies were recruited from epilepsy centers in hospitals or clinics.

Finally, there was variation regarding the type of epilepsy participants suffered from. Participants suffered from absence epilepsy in one study; they were divided into epilepsy and psychogenic epilepsy subcategories in another study, but in the rest of the studies the specific type of epilepsy was not specified.

Table 2. Demographic characteristics of the studies' samples

Study	Country	"n" healthy controls	Population	Mean age	Education mean(years)	Gender	"n" patients	Mean age	Education	Gender
Lutz & Helmstaedter, 2005	Germany	220	adults	41.4	11.8	58% women	184	36	9.6 (mean years)	53% male 47% female
Gao et al., 2014	China	260	adults	34.52	13.16	61.2% women	144	33.39	10.56(mean years)	52.1% male 47.9% female
Walterfang et al., 2011	Australia	N/A	adults	N/A	N/A	NA	154	36.3	tertiary educ. =76 persons	56 male 98 female
Hoppe et al., 2009	Germany	244	adults	42.1	MWT-B IQ mean=115.4	137 women	212	38.1	NR	100 male 112 female
Kurzbusch et al., 2013	Germany	83	adults	38.3	69.9% med educ 20.4 hig educ	54.2% women	240	36	66% med educ 11.3% hig educ	45.4% male 54.6 female
Helmstaedter et al., 2010	Germany	277	children	11.3	N/A	56% women	155	NR	N/A	NR
Kadish et al., 2013	Germany	N/A	children	N/A	N/A	N/A	22	13.3	N/A	11 male 11 female

Note: The abbreviations used: med. educ. = medium education, hig. educ. = higher education, NR = not reported. NA = this characteristic did not exist or was not calculated at all.

*No changes have been made in the way of reporting the characteristics; all information is stated as it was presented in the original studies

Cognitive screening tests

In the seven studies that were included in this review, there were five screening tests validated: EpiTrack, EpiTrack Junior, Neuropsychiatry Unit Cognitive Assessment Tool (NUCOG), Neurocognitive Effects (NeuroCog FX) and the Computerized Cognitive Testing in Epilepsy (CCTE). In detail, one study examined the validity of the EpiTrack screening tool in adults with epilepsy, two studies used the EpiTrack Junior in children, one in children with unspecified epilepsy, and one study in children with absence epilepsy. Two studies examined the validity of the NUCOG in adults. In the other two papers, researchers sought to validate two computerised screening tests: the NeuroCog FX and the CCTE cognitive screening tools. Description of the tools is given in Table 3 and the results found by each study are shown in Table 4.

As seen in Table 4, different types of validity were used by the seven studies. Overall, the three types of validity used by the researchers to compare the index tests with the reference standards were convergent, concurrent and discriminant validity, which may all be considered as forms of the broader category of construct validity (DeVon et al., 2007). More specifically, construct validity is defined as “the degree to which an instrument measures the construct it is intended to measure” (DeVon et al., 2007, p. 156). Regarding the three types that were used by the studies included in this systematic review, concurrent validity was used to define the degree to which the scores on a test being used were correlated with another criterion at the same time point. Convergent validity was used when the goal was to check correlation between tools that measure the same construct, whereas discriminant validity is the ability of a tool to differentiate between different constructs.

Regarding the thresholds which are necessary so that the clinicians know when the patients are potentially in the impairment range, a cutoff point based on optimal sensitivity/specificity in the study sample was suggested for NeuroCog FX, whereas for the EpiTrack and EpiTrack Junior the suggested cutoffs were based on means, standard deviation of the raw scores and frequencies of scores. In the studies of EpiTrack junior in absence epilepsy and NUCOG the researchers used cutoffs set from previous validation studies. Additionally, in the studies of the NUCOG Chinese and CCTE, neither a new cutoff was suggested nor was it mentioned if the researchers used a threshold from previous studies and what it would be; sensitivity and specificity values, PPV and NPV were not reported either, though reliability (test -retest) and/or validity (concurrent) values were provided.

Table 3. Description of the cognitive screening tests

1. *EpiTrack*

- **Type:** paper and pencil test.
- **Administration time:** mean administration duration of 12 to 15 minutes.
- **Points:** maximum score of 45 points.
- **Construction purpose:** to detect the effect of anti-epileptic drugs on patients' cognitive function
- **Functions measured:** working memory, attention and cognitive tracking.
- **Subtests:** Trail-Making Test (numbers), Trail Making Test (numbers and letters), a test of response inhibition, digit span backwards, written word fluency and a maze test.
- **Subtest description:** Trail Making Test (numbers): the person has to track numbers from 1 to 25.
Trail Making Test (numbers and letters): the person has to alternate between the numbers and letters in ascending order.
Response inhibition: the person has to inversely read rows of numbers 1 and 2.
Maze test: the patient has to navigate in a maze like driving a car and change direction when they meet a dead end
Written fluency: the person has to write down as many words as possible in 60 seconds, beginning with a specific letter.
Digit span backwards: patients count backwards until they fail two times.

2. *EpiTrack Junior*:

- **Type:** paper and pencil
 - **Administration time:** mean duration of 12 to 15 minutes.
 - **Points:** the score ranges from 10 to 42 points.
 - **Construction purpose:** to assess any effect of anti-epileptic drugs on children and adolescents.
 - **Functions measured:** Working memory, attention and cognitive tracking.
 - **Subtests:** Trail-Making Test (numbers), Trail Making Test (numbers and circles), a test of response inhibition, digit span backwards, written word fluency and a maze test.
 - **Subtest description:** Trail-Making Test (numbers): the child tracks numbers from 1 to 19.
Trail-Making Test (numbers and circles): the child tracks numbers and circles instead of letters.
Response inhibition: the child has to read two rows of 1 and 2 numbers but inversely (saying number 2 when they see number 1 and vice versa).
Maze test: the child has to find the way out of a maze without lifting the pen from the paper.
Written fluency: the patient says as many words as possible beginning from two specific letters; all types of words are allowed.
Digit span backwards: sequences of numbers given must be repeated in reverse order.
-

3. NUCOG.

- **Type:** paper and pencil.
- **Points:** the patients can score in total up to 100 points (maximum 20 points per domain).
- **Construction purpose:** first constructed as a brief cognitive assessment tool for neuropsychiatric disorders and then validated to epilepsy population specifically.
- **Functions measured:** test a) attention b) visuoconstructive abilities c) memory d) executive functions and e) language.
- **Subtests:** Orientation (time and space), digit span (forward and reverse), overlearned sequence
Drawing reproduction, praxis, orientation left/right, neglect, calculation
Verbal registration, verbal recall, spatial recall, long-term autobiographical recall
Motor sequencing, categorical fluency, abstract thinking, managing interference
Verbal comprehension, verbal repetition, writing, reading, word-finding.

4. NeuroCog FX

- **Type:** computerised neuropsychological screening Instrument
 - **Administration time:** duration less than 30 minutes (maximum 35 min)
 - **Functions measured:** susceptibility to interference effects and cognitive flexibility, figural learning and recognition, verbal learning and recognition, working memory, alertness, selective attention, verbal short-term memory, phonemic literal word fluency.
 - **Subtests:** it consists of eight subtests, namely: Figural Memory, Verbal Memory, Two Back, Simple Reaction, Go/No Go, Inverted Go/No Go, Digit Span, and Phonemic Fluency.
 - **Subtest description:** Figural Memory: the person has to memorise a list of figures presented and then recognize them with yes/no answers.
Verbal Memory: the person is presented with a list of words which they have to memorise and then recognise the words answering with yes or no.
Two Back: the person is presented with digits and they have to press the spacebar when the digit which is presented is the second to the last digit shown.
Simple Reaction task: the person is instructed to press the spacebar when as fast as possible when blue circle occurs.
Go/No go task: the person is instructed to press the spacebar when blue circle occurs and do nothing when a yellow circle occurs, whereas in the Inverted Go/No Go they have to do the opposite (react in yellow and ignore blue circles).
Digit Span: patient must recall the sequence that has been visually presented to them by typing the numbers in the keypad.
Phonemic Fluency: the participant has to name words starting with a random first letter selected by the computer.
-

5. CCTE.

- **Type:** computerised screening instrument.
- **Administration time:** average duration of 30 minutes.
- **Functions measured:** memory and executive functions.
- **Subtest description:** Working memory task: including forwards and backwards; the patient is asked to repeat sequences of numbers with increasing length by typing the letters on the screen.

Visuospatial memory task: the person is asked to touch on the screen named objects which are positioned in specific spatial locations and then remember and recall the location in which each object was presented before.

Focused attention: the patient is presented with simple arithmetic expressions and is asked to calculate the result.

Complex attention and incidental memory: the patients are presented each time with one picture in the center of the screen and has to quickly find it somewhere on the screen and touch it; in the second part they are asked to recognize the pictures which were seen before.

Verbal learning: the patient is presented with word pairs and after the learning trials they are provided with the one word (cue word) and asked to type its pair.

Figural memory: the participants are shown some figures (pieces of which are colored) and have to identify them later when they are presented among other figures.

Table 4. Results of included studies

Study	Index test	Reference standard	reliability	validity	Sens/spec: not for epilepsy group	Summary results	cutoff
Gao et al., 2014	NUCOG (Chinese)	MMSE	.922 ^b	con: .86 ^a		PPV: ? NPV: ?	not for epilepsy group
Helmstaedter et al., 2010	EpiTrack Junior	ratings of parents about children's school performance	.78 ^a	?	sens: ? spec: ?	PPV: ? NPV: ?	≤30
Hoppe et al., 2009	NeuroCog FX	CIT, TMT, maze test, span tests, VLMT, DCS, performance test system, dementia test	.71~.84 ^a	conc: .19~.67 ^a	sens: .54~.65 spec: .69~.75	PPV: .27~.50 NPV: .78~.87	≤28 <85
Kadish et al., 2013	EpiTrack absence	HAWIK-IV: coding, symbol search, letter-number sequencing, block design, digit span, working memory, psychomotor speed, ROCFT: copy, organizational score, VLMT learning, word fluency	?	conc: .37~.78 disc: .08~.37 ^d	sens: .50~1 spec: .39~.50	PPV: ? NPV: ?	first validation cutoffs
Kurzbuch et al., 2013	CCTE	TMT, DCS, VLMT, verbal learning	.40~.79 ^a	conc: .64~.82 ^a	sens: ? spec: ?	PPV: ? NPV: ?	?
Lutz & Helmstaedter, 2005	EpiTrack	Motor sequences, letter cancellation, block design, maze test, mental tation, symbol counting, digit forward, Corsi block tapping, word fluency	.79 ^a	con: .85 ^a dis: .67~.71 ^a	sens: ? spec: ?	PPV: ? NPV: ?	≤28 (mildly imp) ≤25 (severely imp)
Walterfang et al., 2011	NUCOG	Digit span, block design, matrix reasoning, Rey figure, visual reproduction, information, logical memory, similarities, perceptual organization, trail making, DKEFS, vocabulary, verbal comprehension, boston naming test	?	conc: .34~.75 ^c	?	?	<80 (from prior validation)

Abbreviations: ? = not reported, con = convergent, conc = concurrent, disc = discriminant, CIT = test for cerebral inefficiency, TMT = trail making test, VLMT = Rey auditory verbal learning test, DCS = Diagnosticum für Cerebral schädigung – revidiert, ROCFT — Rey–Osterrieth Complex Figure Test. HAWIK-IV — German equivalent of WISC-IV.

^a = Pearson's Coefficient, ^b = Cronbach's α , ^c = Spearman's, ^d = nonsignificant

Note: In the cases that various values were presented (e.g., one for each subtest), values were presented in ranges (~).

In summary, regarding the studies included in this review, there was variation in terms of the number of reference standards used (see the next section). One study (Helmstaedter et al., 2010) did not report validity rates. In three of the six remaining studies, the validity rates were relatively high (Gao et al., 2014; Kurzbuch et al., 2013; Lutz & Helmstaedter, 2005), but in these studies only a limited number of tests were used as reference standards.

Reference standards

The diagnostic criteria for epilepsy do not require cognitive impairment (Fisher et al., 2014). That is, cognitive impairment is not inevitable in epilepsy. The purpose of using a cognitive screening tool in patients with epilepsy is to identify whether cognitive impairment—resulting from epilepsy related factors—is present. Thus, in relation to a reference standard, other tests or measures known to be sensitive to cognitive impairment are required. However, given that there are a very large number of cognitive tests, then it is perhaps to be expected that the reference standards used in validation studies of cognitive screening tools varies considerably.

The most commonly used reference test was the Digit Span (Wechsler, 1997a) as an index of working memory function, which was used in four of the seven studies (Hoppe et al., 2009; Kadish et al., 2013; Lutz & Helmstaedter, 2005; Walterfang et al., 2011). Moreover, three tests were common to three studies. These were the Trail Making Test, which measures scanning, speed of processing, visual search, mental flexibility but also executive functions (Reitan & Wolfson, 1985; Tombaugh, 2004) and which was used in the following studies: Hoppe et al. (2009), Kurzbuch et al. (2013) and Walterfang et al. (2011); a German version of the Rey Auditory Verbal Learning Test (Helmstaedter et al., 2001; Rey, 1958) -which examines verbal learning and memory-, used in the Hoppe et al. (2009), Kadish et al. (2013) and Kurzbuch et al. (2013) studies; finally, subtests assessing verbal learning and memory from Wechsler scales, (Wechsler, 1997a) were used in Kadish et al. (2013), Kurzbuch et al. (2013) and Walterfang et al. (2011) studies.

In addition, verbal fluency was measured using the Regensburger Wortflüssigkeits-Test (RWT; Aschenbrenner et al., 2010) in Kadish et al. study (2013), whereas Walterfang et al. (2011) used the Delis–Kaplan Executive Function System (DKEFS; Delis et al., 2001) to assess the same function. The Diagnosticum for Cerebral Impairment (Weidlich et al., 2001) - which measures figural memory - was used in two studies, namely by Kurzbuch et al. (2013) and Hoppe et al. (2009). The Maze Test (Chapuis et al., 1992), which measures anticipation and planning, was also used in two studies: in Lutz and Helmstaedter (2005) and Hoppe et al. (2009). The Block Design which examines visuoconstructional functions (Wechsler, 1997a) was used in the studies of Lutz and Helmstaedter (2005) and Walterfang et al. (2011). Also, Kadish et al. (2013) and Walterfang et al., (2011) used the Rey Osterreith Complex Figure Test

(ROCFT; Osterreith, 1944; Rey, 1941) to measure visuo-constructional abilities and non-verbal memory.

Finally, there were subtests or screening tools that were utilized by one study only. In the validation of NeuroCog FX (Hoppe et al, 2009) the index test was compared with three tests: the Performance Test System which measures word fluency (Horn, 1983), the Dementia Test, measuring memory, verbal fluency, orientation and praxis (Kessler et al., 1988), and the Test for Cerebral Insufficiency (CIT; Lehrl, 1997). Also, in the validation of EpiTrack (Lutz & Helmstaedter, 2005) additional tests were used to examine the convergent validity, such as Mental Rotation, which examines spatial- visualization abilities (Vandenberg & Kuse, 1978), Corsi block tapping, assessing non-verbal learning and memory (Corsi, 1972) and other, non-standardised tasks assessing attention and executive functions such as symbol counting, motor sequences and letter cancelation. Additionally, the Chinese version of NUCOG (Gao et al., 2014) was the only screen validated against a cognitive screening tool, specifically the Mini Mental State Examination which assesses orientation to time and place, registration and recall of three words, attention and calculation, language, and visual construction (Folstein et al., 1975). In the validation of the English NUCOG (Walterfang et al., 2011), several tasks from the Wechsler intelligence and memory scales (WAIS/WMS; Wechsler, 1997a; 1997b) were also used, specifically: Matrix Reasoning, Vocabulary, Information, Similarities, Visual Reproduction, and Logical Memory. The Boston Naming Test (Kaplan et al., 1976) examining word retrieval and the Wechsler Test of Adult Reading (Wechsler, 2001) for the assessment of premorbid IQ were used for estimating IQ. Finally, for the validation of EpiTrack Junior (Helmstaedter et al., 2010), the performances of the patients on the index test were compared to the parents' ratings of their children's school performances.

Quality assessment

The studies were assessed in terms of quality of diagnostic accuracy, risk of bias and applicability as rated by the QUADAS-2 tool (Whiting et al., 2011). Each of the four domains of QUADAS-2 tool was marked as having low, high or unclear risk of bias and concerns of applicability to this review with reference to specific signaling questions. Thus, regarding applicability concerns, all seven studies had low risk in all the three domains (patient selection, index test, and reference standard). Regarding risk of bias, six studies were characterised as low risk in the patient selection domain and one study as high risk. However, in the index test, reference standard and flow and timing domains, most of the studies were marked as having either high risk or as unclear. The detailed description of the studies in terms of QUADAS-2 assessment is given in Table 5.

According to the conclusions of the authors of the studies reviewed, all five tools –NeuroCog FX, CCTE, EpiTrack, NUCOG, and EpiTrack Junior– proved valid for use in epilepsy patients. More specifically, NeuroCog FX and CCTE were suggested for use in clinical and research settings; Hoppe et al. (2009) suggested that NeuroCog FX provides reliable and valid cognitive assessment, while Kurzbuch et al. (2013) supported that CCTE provides effective screening of memory and executive functions and discriminates different levels of impairment in relation to medication effects. Lutz and Helmstaedter (2005) suggested that EpiTrack provides prompt results, facilitating the diagnostic process. Additionally, Gao et al. (2014) reported that NUCOG was a reliable and sensitive tool, able to differentiate cognitive decline in certain seizure types. Finally, EpiTrack Junior was suggested by Helmstaedter et al. (2010) as a valid and reliable tool to assess executive functions in children with epilepsy and absence epilepsy. However, it is possible that the authors made those conclusions based only on reliability and validity measures of the studies. Perhaps, additional diagnostic accuracy values could be reported by the authors, for the quality of the studies to be improved. As shown in Table 4, only one of the seven studies provided Positive Predictive Values (PPVs) and Negative Predictive Values (NPVs) and only two studies in total provided sensitivity and specificity rates. Despite important information missing, the tools were considered as valid for use.

DISCUSSION

The purpose of this review was to summarise the existing literature on cognitive screening tools in patients with epilepsy, to investigate the quality of the studies, and to identify priorities for future research.

In total, seven studies were found, in which researchers examined the validity of screening tools in detecting cognitive impairment in epilepsy patients. The total number of screening tools used was even lower than the studies found, namely five – the EpiTrack and the EpiTrack Junior version for children, the NUCOG, the NeuroCog FX, and the CCTE– which is a low number, compared to the number of validation studies conducted and screening tools that have been validated for other conditions, e.g., to screen for depression in epilepsy where sixteen tools were identified (Gill et al., 2017) or cognitive impairment in dementia where 39 screening tests were identified (Cullen et al., 2007).

Table 5. QUADAS-2 results

Study	RISK OF BIAS						APPLICABILITY CONCERNS		
	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD	INDEX TEST	REFERENCE STANDARD
Lutz & Helmstaedter, 2005	LOW RISK	UNCLEAR	UNCLEAR	UNCLEAR	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK
Gao et al., 2014	LOW RISK	HIGH RISK	UNCLEAR	UNCLEAR	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK
Walterfang et al., 2011	LOW RISK	UNCLEAR	UNCLEAR	HIGH RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK
Hoppe et al., 2009	LOW RISK	HIGH RISK	UNCLEAR	HIGH RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK
Kurzbnch et al., 2013	LOW RISK	UNCLEAR	UNCLEAR	HIGH RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK
Helmstaedter et al., 2010	LOW RISK	HIGH RISK	HIGH RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK
Kadish et al., 2013	HIGH RISK	UNCLEAR	UNCLEAR	UNCLEAR	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK

With regards to the samples used, there was heterogeneity among the studies concerning the employment of healthy controls group, the number of participants, the age, the mode of presentation of the participants' education, as also the types of epilepsy in which the samples belonged to. All these factors indicate a great variance in both the epilepsy and the comparison groups used by each study, making comparisons across studies hard.

As far as the mode of administration of the test is concerned, there were both paper and pencil tests, and computerised tests. Validating both types in epilepsy populations is important for clinicians to have an idea about the applicability of the specific screening tests in epilepsy. Paper and pencil tests remain the most commonly used cognitive tests, but computerized tests are being used more and more in research and clinical settings. However, the grading in paper and pencil tests can be possibly prone to clinician's subjectivity. On the other hand, grading in computerized tests is objective and consistent, but other factors can possibly intervene, such as motor problems of participants, which are common in neurological disorders, and indeed in epilepsy.

In addition, there were substantial differences regarding the subtests that the screening tools are comprised of, and consequently the functions being assessed varied among the studies. For example, EpiTrack is focused on executive functions and attention, whereas NUCOG, NeuroCog FX, and CCTE additionally assess memory. Moreover, NUCOG also assesses visuo-constructional abilities and language. This raises the question of the ability of the screening tools to examine multi-dimensionally the cognitive status of the patients. It also raises questions of false negatives, as the screening tools are used to detect cognitive change in the patients; consequently, if the patient has a cognitive impairment in one of the domains which are not examined by the screening tool, false negatives will occur.

Finally, the studies included in this review could provide more information regarding diagnostic accuracy. As shown in Table 4, there were studies which did not report one or more of the following: reliability, validity, sensitivity and specificity, positive/negative predictive values.

The methodological quality assessment highlighted limitations in the literature. While the applicability concerns rating was defined as "low risk", in the risk of bias section the quality of the studies was relatively poor, especially in the index test, reference standard and flow and timing sections. In these sections, all but one study had unclear or high risk of bias, indicating that important information regarding processes and methods was missing or that the results in relation to the diagnostic accuracy of the tools might be questioned.

This review is the first systematic review of cognitive screening tests being used in epilepsy and provides clinicians with information on existing validated tools on epilepsy patients, including diagnostic accuracy features which may help them decide the most appropriate tool to use. However, a significant limitation is the heterogeneity among the studies, in terms of reference standards, sample sizes and characteristics

which did not allow for meta-analysis. In addition, the lack of reporting of diagnostic accuracy features, such as sensitivity and specificity, PPV and/or NPV and/or cutoff scores limits the conclusions that can be drawn.

Conclusions

Relatively little research has been done in the field of cognitive screening tools in patients with epilepsy. The five screening tools for which validity has been examined would make the choice of the appropriate screening tool easier for clinicians if more diagnostic accuracy features had been provided. More generally, there was significant heterogeneity among the studies regarding sample sizes and sample demographics (e.g., children or adults), different clinical characteristics of patients (all epilepsy patients included in one group, patients separated in groups of epilepsy and non-epileptic seizures or include only patients with a specific sub-type such as absence epilepsy) or different mode of administration (paper and pencil or computerized).

However, based on the available data, it seems that EpiTrack could be the preferred screening tool to start with, given that it is the only one specifically constructed for and validated on both adults and children with epilepsy. Moreover, it provides specific cutoff points and a more satisfactory level of reliability compared to the rest of the tests. It is, therefore, suggested that clinicians start the assessment using EpiTrack for screening purposes and combine it with the administration of tools assessing more cognitive functions if the patients' performance and clinical image demand so.

Future directions

There is a clear clinical need for tools that accurately screen for the presence of cognitive impairment in people with epilepsy, but more studies are necessary, with more detailed reporting of results and diagnostic accuracy features, to confirm which tests are useful to guide clinicians' choice of cognitive assessment instrument. Also, as the only screening test validated in children and adolescents is EpiTrack, the validation of more tools assessing more cognitive domains would be beneficial.

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