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Cognitive Functioning in Children with Self-Limited Epilepsy with Centro-Temporal Spikes (ECTS): A Systematic Review and Meta-analysis

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Please find supplementary material attached as separate files. Forest plots for each CHC factor have been summarized in a single table – please see supplementary material for individual plots. Other supporting information includes: Study Quality Ratings Table, Neuropsychological Tests assigned to CHC factors, Funnel Plots and Meta-regression Table.

Abstract

Objective: It is now well appreciated that Benign Epilepsy with Centrotemporal Spikes (BECTS or more recently ECTS) is associated with a range of cognitive and behavioral disturbances. Despite our improved understanding of cognitive functioning in BECTS, there have been to date no efforts to quantitatively synthesize the available literature within a comprehensive cognitive framework.

Methods: The present systematic review and meta-analysis was conducted according to PRISMA guidelines. Forty-two case–control samples met eligibility criteria comprising a total of 1237 children with BECTS and 1137 healthy control children. Univariate, random-effects meta-analyses were conducted on eight cognitive factors in accordance with the Cattell-Horn-Carrol (CHC) model of intelligence.

Results: Overall, children with BECTS demonstrated significantly lower scores on neuropsychological tests across all cognitive factors compared to healthy controls. Observed effects ranged from 0.42 to 0.81 pooled standard-deviation units, with the largest effect for long-term storage and retrieval (*Glr)* and the smallest effect for visual processing (*Gv*).

Significance: The results of the present meta-analysis provide the first clear evidence that children with BECTS display a profile of pervasive cognitive difficulties and thus challenge current conceptions of ECTS as a benign disease or of limited specific or localized cognitive effect..

Keywords: Benign Rolandic epilepsy, Childhood epilepsy, Focal epilepsy, neuropsychology, cognition

[Main text]

Rolandic Epilepsy (RE) is the most common form of childhood idiopathic focal epilepsy, estimated to account for up to 16% of all childhood epilepsy cases.[1] With the typical age of onset of 6-10 years of age, patients with RE experience relatively infrequent focal seizures with retained awareness, presenting predominately as nocturnal, hemi-facial motor seizures with sensory features that can secondarily generalize. Also historically

referred to as Benign Epilepsy with Centro-Temporal Spikes (BECTS), the EEG marks the presence of stereotyped high voltage blunt spike-slow wave discharges in the centro-temporal, rolandic, region.[2] Current understanding classifies the etiology of BECTS as provisionally unknown.[3] While there is a presumed genetic underpinning, tentatively related to the centro-temporal spike component[4], poor concordance in monozygotic twins indicates that genetic factors are not paramount.[5] As such, epigenetic and environmental factors may account for the expression of the epileptic syndrome.

Although atypical expressions can manifest, the characteristically benign nature of the condition is appreciated in relation to the tendency for patients to achieve complete seizure remission in the overwhelming majority of patients.[6] However, given the pervasive and often frequent occurrence of interictal cortical hyper-excitability, notably active during sleep, and more generally over the course of a sensitive developmental period, a host of studies have explored the impact of BECTS on behavior and neuropsychological functioning.[7] As such, a series of studies have revealed elevated prevalence of cognitive deficits, behavioral disturbance, learning disorders, specific language impairment, speech-sound disorders and educational and academic problems for children with BECTS. [8-9] Accordingly, revised terminology avoid the erroneous implication of the benign nature of the condition, replacing "benign" with self-limited. Henceforth we will use the abbreviation ECTS in place of BECTS. Children with ECTS are also at higher risk of developing ADHD symptoms and externalizing behaviors compared to controls[10-12]. Rates of psychopathology are elevated, with studies demonstrating 64.5%[13] and 81% [14] of ECTS children displaying at least one DSM-IV defined psychological disorder diagnosed with the respective DSM-IV or Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS) criteria, Given the increased risk of a range of disruptions, it is not surprising that quality of life is also reduced in these children.[15]

In relation to cognitive outcomes, a common contention in the literature is that general intellectual functioning in children with ECTS is within normal limits although below their healthy peers[7]. Systematic reviews have indicated notable difficulties associated with verbal and visual memory[16] and attention directed-processes[17], although most reviews also report disturbances in other cognitive domains such as processing speed, visuo-spatial skills, visuo-motor coordination and executive functioning.[7, 18]

A research focus on language function and processing of verbal and auditory information stems from the apparent association between the location of epileptiform activity in ECTS and a cortical region critical for language functioning, that is, the Rolandic region.[16] Accordingly, studies have implicated a variety of different expressive and receptive language processes, some arguing for widespread language dysfunction[19] while others advocate circumscribed language deficits.[20] This line of reasoning has prompted some researchers to propose that memory deficits may even result from a dysfunctional language system, such that there is difficulty in encoding and organizing the verbal information into memory for long-term storage.[16]

To our knowledge, there has been one effort to quantitatively synthesis cognitive outcomes in ECTS whereby Smith, Bajomo and Pal (2015) recently conducted a meta-analysis on language and literacy skills in children with ECTS. The authors found moderately large differences in all factor aspects of language function reviewed, including single-word reading, phonological processing, expressive and receptive language. While the Smith et al. (2015) review is an important contribution providing clear evidence of an increased likelihood of language deficits in children with ECTS, it is still unclear where these deficits sit in the broader neuropsychological profile. It is also noteworthy that the authors did not assess for methodological quality of studies[21].

Although there is a consensus that children with ECTS are at a higher risk of cognitive impairment, explaining and attributing the findings is also not so clear. The impact of various specific or broader disease-related features have been explored, for example age of onset[22] electrophysiological characteristics (see [16]) and anticonvulsant medication effects (see [7]) etc., cognitive impairment in epilepsy is likely a multi-factorial phenomenon[23]. Nevertheless, a coherent understanding of the profile of cognitive deficits, grounded in strong psychometric theory, may provide a necessary cornerstone for exploring the apparent heterogeneity of deficits.

The available research is limited by several methodological factors.[17] Many studies include small sample sizes, are inconsistent in their inclusion or exclusion criteria, lack control groups or are poorly controlled, or fail to adequately report data. As a result, studies have increased risks of sampling, spectrum or reporting biases. In addition, several studies assessed a limited scope of cognitive ability, thereby increasing the likelihood of confirmation bias or attributing poor performance to localized dysfunction. As such, mixed

findings are reported across the cognitive factors and a clear picture of the neuropsychological profile in ECTS remains to be elucidated.

There have been to date no efforts to quantitatively synthesize the available literature within a cohesive and comprehensive cognitive framework. Accordingly, the current study conducted a systematic review and meta-analysis on cognitive outcomes in children with ECTS, in accordance with a widely accepted, comprehensive and empirically validated framework of cognition, the Cattell-Horn-Carrol (CHC) model of intelligence.[24-27] The CHC model has been recently applied to examining cognitive functioning in idiopathic or genetic generalized epilepsy.[28] and has been shown to provide a rational, parsimonious taxonomy of cognitive abilities in diverse neuropsychological batteries, including executive function.[29,30] We hypothesized that children with ECTS would exhibit deficits in cognitive functioning compared to healthy controls and we further explored the magnitude of any difficulties. We investigated whether there is a particular profile of neuropsychological functions which are preferentially affected, and we explore whether any methodological or clinical factors can explain the variability in cognitive effects between studies.

Methods

Protocol registration

The systematic review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO: registration number CRD42015024457). The review was conducted according to PRISMA guidelines. [31]

Search strategies

A search for articles was conducted using Medline and Scopus databases for articles published up to and including 31st of December 2016. Keywords were entered in terms of syndrome *(rolandic epilepsy, benign epilepsy with centrotemporal spikes, BECTS, BCECTS, BRE or BECRS*) and neuropsychological outcomes (*cognitive, cognition, neuropsychology, neuropsychological, intelligence, language, memory, attention, executive function*). The reference lists of eligible articles were also searched for additional studies.

Selection criteria

Studies adhering to all of the following eligibility criteria were included: (a) original research published in a peer-reviewed journal, (b) case-control or cohort studies with both a sample of participants with a diagnosis of ECTS and a healthy aged-matched control group (c) participants were between the ages of 6-16 years of age at testing to facilitate group homogeneity and comparability of outcome measures, (d) outcomes included any factor of cognitive functioning measured by published neuropsychological tests. Studies were excluded if (a) the patient group contained those with rolandic discharges without a positive clinical history of seizures (b) the patient group included a heterogeneous sample of epileptic syndromes, (c) the control group was a non-epilepsy diagnosis-positive sample (rather than healthy controls); (d) full-text article was not available or not available in English; (e) means and standard deviations for test data were not available. References included in the systematic review and meta-analysis are identified in the reference list with an asterisk.

Data Extraction

Neuropsychological test data was extracted from the included studies in the form of test means and standard deviations. Tests were classified in accordance with the CHC model broad factor in which the test was deemed to load most highly (details of the classifications are available in the supplementary material. Test allocation to CHC factor was drawn from the latent variable or factor structure of tests as presented in prior literature and the judgement of two independent raters (SW and SB). More precisely, tests were allocated using the detailed operational definitions of CHC constructs by McGrew (2009). To facilitate continuity between studies, many tests were allocated to their respective factors consistent with the previous review b Loughman, Bowden and D'Souza (2015).[28] The CHC model of intelligence is the most comprehensive and empirically validated model of human cognition.[24-30]The CHC framework functions on a hierarchical, three-stratum model. Foremost, an overarching factor of general intellectual functioning (*G*) underscores several broad cognitive abilities including, however not limited to, acquired knowledge (*Gc*), fluid reasoning (*Gf*), working memory capacity (*Gsm*), processing speed (*Gs*), and long-term storage and retrieval (*Glr; see Table 1*)[42]. Further, a host of narrow abilities are subserved under the broad factors.

While the CHC framework does not explicitly refer to 'executive functions', they remain to be a construct of importance for many researchers and clinicians.[30] As such, the CHC model accounts for tests of executive function as several broad stratum abilities or as a conflation of various CHC factors.[29-30] Lexical retrieval, otherwise referred to as verbal fluency, is also commonly regarded as an executive function. In traditional CHC theory, fluency is conceptualised as a narrow ability of *Glr,* however recent investigation suggests that fluency may be best represented as an independent broad factor; representing retrieval processes independent of encoding.[29] Accordingly, the current study conceptualised fluency (*Gr*) as a broad stratum ability.

In terms of the extraction of neuropsychological test data:

- Where a single study reported on multiple tests reflecting the same underlying broad CHC factor (i.e. digit span and block span*)* each test was extracted and pooled within the study for the respective factor (i.e. *Gsm).*
- Where a test included multiple outcomes for the same set of stimuli, a single representative outcome was chosen (i.e. RAVLT delayed recall for RAVLT).
- Where separate neuropsychological test data was reported for subgroups within a study (i.e. EEG focus[32-34]; AED presence[35]; IED presence, [36] etc.), data for each group was extracted and pooled within the study.
- Where test data was collected and reported across multiple time-points, information was extracted for patients and controls at the first time-point only.[32,37-39] Given the paucity of longitudinal studies, data in the current study was restricted to outcomes during the active epilepsy phase.
- Where a study included multiple control comparisons (i.e. community controls and patient siblings)[35], community controls were selected preferentially.
- Where there were multiple papers containing overlapping, duplicate samples with overlapping neuropsychological tests a single paper was chosen. This decision was based on the most comprehensively reported and representative paper. However, where there were multiple papers with duplicate samples containing different neuropsychological tests, measuring different cognitive factors, both papers were included and considered as a single study (e.g. Riva et al, 2008 and Vago et al., 2008; Lopes et al., 2013 and Lopes et al., 2014).

A number of clinical variables were also extracted from included studies. This included case and control sample sizes; use of ILAE diagnostic criteria; mean sample age of epilepsy patients; mean sample age of epilepsy or seizure onset; centro-temporal spike focus and proportion of children on anti-epileptic medication (AED). Where descriptive statistics weren't provided but individual patient data was presented, means and standard deviations were computed. Where enough data was available, meta-regression analyses were conducted on clinical variables.

Statistical analysis

Meta analyses were conducted with Comprehensive MetaAnalysis Version 2 software (CMA).[43] Effect sizes were computed for each study and pooled for each cognitive factor. That is, each study produced an effect size reflecting the magnitude of Standardized Mean Difference (SMD) in neuropsychological test data between children with BECTS and healthy control children. Standard guidelines were used for interpreting effect size magnitude (SMD = 0.20, *small effect*; SMD = 0.50, *moderate effect*; SMD = 0.80, *large effect)*.[44-45] Point estimate interpretation was supplemented with the associated SMD confidence intervals. For each cognitive factor, a random effects meta-analysis was conducted. The random effects model provided an estimate of the overall mean effect size and its confidence interval, under the assumption that the studies were conducted independently[44], and that each reflect a random sample of cognitive abilities and patients.

The distribution of effect sizes from the included studies was examined with Q test for each factor such that a significant Q statistic rejects the assumption of homogeneity. Importantly, a non-significant Q does not necessarily equate consistency among effects nor does the Q statistic provide a reliable measure of magnitude for between study heterogeneity.[44] Computation of tau-squared (T^2) provided a measure of the dispersion or variance of true effects between studies.[44] Further, the I squared (I^2) statistic was computed, which describes the percentage of dispersion in effect estimates that is due to real rather than spurious.[44]

Assessment of Methodological Quality

No gold standard assessment of methodological study quality for observational research currently exists.[46] The current study adopted the Newcastle-Ottawa Scale (NOS) as a

tool to quantify the methodological quality of included studies.[47] The NOS is an instrument that assesses the quality of non-randomized observational studies and has been implemented in several published systematic reviews and/or meta-analyses including case-control and cohort studies. The scale incorporates a star system in which each study can receive up to a maximum of nine stars if all criteria have been satisfied within three categories: selection, comparability and exposure/outcome.

The selection variables address the validation and representativeness of both the cases and controls, thereby providing a measurement of selection bias. Alternatively, comparability determines sample matching criteria, that is, whether a given study controlled for age and/or some additional factor by design. The third variable exposure, foremost evaluates the quality (i.e. blinding) and similarity of test data ascertainment as to help reduce possible performance bias. In addition, the exposure variable also addresses sample representativeness via assessing whether a study provides adequate information regarding sample response rates for testing (i.e. descriptions of non-response or refusal-to-participate rates).

While research suggests that it possesses adequate test-retest reliability, inter-rater reliability is typically poor and others have even questioned the validity of the items.[48] As such, it's application in the current study was to quantify methodological quality as a relative measure rather than an absolute measure of quality. Quality assessment was further examined for any additional risks of bias not otherwise captured by the NOS. To assess for publication bias, funnel plots were generated for each cognitive factor in which standard error of the intervention effect estimate was plotted against study sample size.

Results

Study Demographics

After removing duplicate articles (see Figure 1), 437 papers were screened for eligibility. Screening on the basis of title and abstract excluded 297 papers. Of 140 remaining studies, forty met the eligibility criteria. Two additional papers were identified as duplicate samples, although containing data for different cognitive factors[34, 39] and were therefore included and treated as one sample of ECTS children. Subsequent to initial screening, many studies were excluded because of comprising a mixed epilepsy sample or samples with centrotemporal spikes without epilepsy (n=8), full text not available (n=13) or unavailable in English (n=4), no control group (n=24) or a non-epilepsy positive diagnosis control group (i.e. migraine or peripheral nervous system disorders; n=3), insufficient data reporting (n=18), no neuropsychological tests used or tests which were not adequate published neuropsychological tests (n=11), older patient samples (>16 years, n=3), or were a sample described in another paper (n=15). Where data was incomplete, not reported or full text was unavailable, authors were contacted via email to request data. This resulted in the additional inclusion of data from only one study.[49]

Demographic and disease related variables were varied across the included studies and studies were mixed in terms of the reported variables. Included studies reflected a wide-range of different languages and cultural backgrounds. The total sample consisted of 1188 children with ECTS and 1074 control participants. The mean age of the BECTS samples was 9.82 (.96) with only three studies not reporting mean sample age.[35,50-51] In total 30 studies reported on age of onset, with mean age of onset ranging from 4.17 to 9.6. Most studies defined age of onset in terms age at first seizure, however some defined it in terms of age of epilepsy onset (i.e. age at diagnosis) while other studies were unclear. Importantly, age of onset is often difficult to estimate given the nature of the semiology. Eleven studies included ECTS samples who were not on any anticonvulsants at the time of neuropsychological assessment and most studies contained some proportion of ECTS children who were on an anticonvulsant, predominately monotherapy with carbamazepine, sulthiame or valproate.

Study Quality

The overall quality rating score, as per the NOS, ranged from 1 to 9, with a mean score of 5.4 (SD = 1.68; see supplementary material for table of individual study NOS quality ratings). Overall, the quality of studies was moderate with many studies demonstrating several potential methodological sources of bias. In terms of the selection of cases and controls, studies were mixed in their potential for selection and representativeness bias. For patient samples to be considered well defined and externally validated, studies were to 1) explicitly refer to the use of International League Against Epilepsy (ILAE) diagnostic criteria OR otherwise explicitly refer to each core ILAE criterion (including: presence of stereotyped high voltage blunt centro-temporal spikes which activate during sleep, normal background EEG, experienced typical BECTS seizures and no other neurological features) and 2) provide external reference to electrophysiological information. Overall, 68% of studies met these conditions for case definition and validation. However, around half (45%) of the included studies failed to sample consecutively or provide clear information regarding the sampling of the patient group (i.e. all cases in a defined catchment/s or time-frame) and thus potentially pose risks of sampling bias.

Potential sources of representativeness bias could lie in the variability of inclusion and exclusion criteria, differing across studies. Included studies were mixed in terms of excluding based on IQ, with exclusion IQ ranging from >60 to >90. Given that poorer cognitive function is somewhat expected in this population, exclusion based on overall intellectual function could likely underestimate cognitive outcomes in these children. Likewise, exclusion of cases based on psychiatric co-morbidity (i.e. presence of developmental disorder or clinically significant psychopathology), as was an exclusion criterion in 15 studies, could also lead to misrepresentation of cases given the high prevalence psychiatric comorbidity in this population.[10, 13-14]

In relation to control samples, many studies were unclear on the sampling (47%) and health status details (27%) for control participants. The case and control samples were typically well matched for age on design, or otherwise revealed non-significant differences. Moreover, around half of the samples (58%) also matched subjects for an additional factor, most commonly gender or socioeconomic status A significant source of bias existed in the non-blinding, or non-reporting, of case-control status during assessment. This was notably

poor given that the status of children with ECTS is not readily apparent. As such, few studies blinded test administrators of case-control status (25%), with most of these studies reflecting computerized assessment. Positively, most studies used the same neuropsychological testing methods for both cases and controls (90%). Evidence of reporting bias was evident, as many studies failed to comment on response rate (38%).

Results of Meta-Analyses

Random effects meta-analyses for all cognitive factors revealed a significant standardized mean difference indicating poorer cognitive function in children with ECTS, with effect sizes ranging from moderate to large (see table three).

Data for the factor of general intellectual ability, as indexed by the CHC factor *G*, was pooled from 27 studies. All these studies included only one measure of overarching cognitive function. Most studies assessed this factor with the Wechsler full scale IQ, with some variation in the edition used. The standardized mean difference revealed a moderate effect indicating significantly lower general intellectual ability for children with ECTS compared to normal controls (SMD −0.62, 95 % CI −0.83 to –0.41, p <.001). The acquired-knowledge factor (*Gc*) contained the highest number of studies (k=29). This factor assessed a wide-range of tests examining language skills, verbal functioning and overall acquired knowledge, comprising a range of narrow *Gc* abilities. The meta-analysis for Gc showed a moderate effect size between children with ECTS and controls (SMD −0.79, 95 % CI −1.00 to –0.57, p <.001). There was a similar, although large effect size, between cases and controls for long-term storage and retrieval based memory function (*Glr*), pooled from 12 studies (SMD −0.81, 95 % CI −1.13 to –0.48, p <.001). Relatedly, results from the fluency factor showed a similar moderate-large effect size (k=10, SMD −0.79, 95 % CI −1.18 to –0.40, p <.001).

Fluid reasoning (k=27, SMD −0.54, 95 % CI −0.74 to –0.33, p <.001), speed of information processing (k=22, SMD −0.60, 95 % CI −0.85 to –0.34, p <.001) and short-term memory (k=18, SMD −0.52, 95 % CI −0.80 to –0.24, p =.001) factors revealed moderate standardized mean differences between children with ECTS and controls. Visual processing demonstrated a significant, although small effect showing poorer processing in children with ECTS compared to controls (k=12, SMD −0.42, 95 % CI −0.71 to –0.13, p <.001). Despite

the observed differences in the effect size point estimates, all cognitive factors differed significantly from zero and displayed overlapping confidence intervals.

All meta-analyses revealed significant Q statistics, indicating the presence of significant heterogeneity between studies. The I squared statistic ranged from 64.84 to 80.36, demonstrating that a substantial percentage of the variability in effect estimates was due to heterogeneity between studies. Visual inspection of funnel plots for each cognitive factor revealed approximately symmetric plots and thus no clear evidence of publication bias (see Supplementary Material for funnel plots).

To examine sources of variability between studies, several meta-regression analyses were undertaken with CMA on clinical variables (mean age at assessment, mean age of onset, proportion of sample on anticonvulsants), study quality (overall NOS quality rating) and study exclusion criteria based on IQ (coded categorically as either Yes or No) and/or presence of psychiatric or developmental disorder (coded categorically as either Yes or No; see table two). Given the variability in the reporting of clinical information, a separate meta-regression was run for each variable across each cognitive factor, as opposed to analyses with multiple factors, to ensure an adequate number of studies per analysis. Adjusting for multiple comparisons, all analyses were non-significant (all p's>.001). The total NOS rating was found to explain 30% of the variance in effect sizes between studies in the short-term memory (*Gsm*) factor, which approached corrected significance (Q (1) = 6.04, p = .014, R^2=.30), showing larger effects for studies with higher quality.

Discussion

Summary statement main results

While it is the general consensus that children with ECTS have poorer cognitive outcomes compared to controls, this is the first study to systematically review and quantitatively synthesize the literature in terms of a comprehensive model of cognition. All cognitive factors assessed, covering many of the major broad cognitive factors commonly assessed by clinicians and researchers[24,30], revealed significant effects indicating poorer outcomes in ECTS children compared to healthy controls. More precisely, the cognitive factors of Acquired Knowledge (*Gc*) and Long-term Storage and Retrieval (*Glr)* demonstrated large effects while the remaining factors of General Intelligence (*G*), Fluid Intelligence (*Gf*), working memory capacity (*Gsm*), Processing Speed (*Gs*), Visual Processing (*Gv*) and Fluency (*Gr*) showed effects in the moderate range. Despite the observed differences in the effect size point estimates, all cognitive factors differed significantly from zero, thus indicating likely deficits, and displayed overlapping confidence intervals. Overall, the results of the present meta-analysis indicate that children with ECTS display a variable profile of diffuse cognitive deficits and thus challenge current conceptions of ECTS as a benign disease or of limited specific or localized cognitive effect.

Results in context of literature

To date, a common assertion is that children with ECTS display normal-range IQ on a background of specific cognitive difficulties.[7,18] The results of the present quantitative synthesis indicate that these children have poorer outcomes across a range of cognitive factors, compared to healthy peers, notwithstanding difficulties in the overarching factor of general intellectual functioning. Interestingly, the observation of normal-range IQ in children with ECTS may be at least partially attributed to many studies excluding children based on low IQ.

Language dysfunction is recurrently raised as an issue of concern in the ECTS literature.[19,20, 67] In a recent meta-analysis, Smith, Bajomo and Pal (2015) reported poorer auditory processing, single-word reading and expressive and receptive language in children with ECTS compared to control data, with moderate effect sizes. The findings of the present analysis similarly revealed a large effect for poorer

outcomes in the acquired-knowledge *Gc* factor – a broad construct reflecting acquired verbal knowledge and language-based abilities.[21] Not surprisingly, many of the studies included in Smith et al. (2012) and the current *Gc* meta-analysis were overlapping. Smith et al. (2012) showed moderate effects for narrow *Gc* abilities (expressive and receptive function) as well as auditory processing (*Ga*) and reading ability (*Grw)*. The current findings extend the findings of Smith et al. (2012), supporting the notion of widespread cognitive deficits associated with ECTS.

In addition to language deficits, systematic reviews have concluded that children with ECTS display worse memory[16] and attentional functioning[17] compared to normal controls. As such, the results of the present study provide quantitative support for these contentions, in addition to poorer cognitive outcomes in other major cognitive factors, including visual processing, verbal fluency, processing speed and fluid reasoning. Interestingly in the latter qualitative review, Kavros et al (2008) allocated different tests within attention-based theory. The authors concluded that there was deficit in all theoretical attention systems including alerting, orienting and executive networks, thereby suggestive of a widespread functional cortical disturbance.[17] Within a comprehensive model of cognition, the same types of "attentional tests" were assigned predominately to CHC factors related to short-term memory (*Gsm*), processing speed (*Gs*) and fluid intelligence (*Gf*). In this way, the conflation of the attentional factors within the Posner model framework is avoided.

Loughman, Bowden and D'Souza (2014) showed a comparable profile of diffuse cognitive difficulties in individuals with idiopathic/genetic generalized epilepsy (IGE) compared to controls, which was largely independent of IGE subtype. However, IGE represents a heterogeneous epileptic syndrome for which there is a *generalized* electrophysiological disturbance, whereas ECTS reflects a *focal* epileptic syndrome with a characteristic presentation and a circumscribed electrophysiological disturbance.[2] Considering the focal nature of ECTS, both types of epilepsy demonstrate a pattern of diffuse, yet variable, cognitive deficits. Indeed, research has shown that different forms of childhood focal epilepsies with different locations of electrophysiological disturbance are associated with widespread cognitive difficulties, including childhood frontal lobe epilepsy[40] and temporal lobe epilepsy.[78] This

converging evidence may suggest a considerable impact of the overarching epileptic disease process.

Moreover, ECTS is an aged-defined epilepsy with a fairly circumscribed age of onset which tends to remit in adolescence. It is therefore clear that maturational factors are important in the development and expression of the disease.[80] Just as normal endogenous neural activity interacts with the environment to foster cognitive development, recurrent epileptiform activity will also likely influence and interfere with brain development. Greater neuroplasticity in children in combination with less functionally specialized neural networks sets the scene for a more dynamic influence of pathological processes.[77] As well, it is increasingly recognized that cognitive functions, especially high-level multi-determined intellectual abilities are broadly represented by complex neural networks.[81] Recent evidence with resting state-fMRI demonstrates systemic brain disorganization in ECTS such that reduced functional connectivity in the Rolandic region influences large scale brain networks.[12] As such, this hypothesis of widespread cortical dysfunction in ECTS is compatible with the current cognitive findings.

Study limitations

One must consider the appropriateness of addressing cognitive functioning at the level of broad stratum abilities. An overarching limitation inherent to this approach of data synthesis is the conflation of narrow abilities into underlying latent constructs and therefore the inability to reveal any potentially narrow, more specific deficits.[17] However, limited available studies with small sample sizes and the diversity of neuropsychological tests used, somewhat impedes the feasibility of synthesizing narrower abilities which are assessed less reliably. As well, not all general intelligence measures include processing speed (e.g., the WASI) and this limitation is a caution on interpretation of the general intelligence effects, which are trait heterogeneous.

Although it was not surprising given the disparate body of literature, the effects for each cognitive factor were associated with significant heterogeneity between studies. The current paper was not able to quantitatively explain the observed heterogeneity between studies. The various meta-regression analyses (i.e. proportion

of sample population on medication, mean age, mean age of onset, study exclusion criteria) did not demonstrate any significant effects while accounting for multiple comparisons. Importantly, these analyses must be viewed with caution, given that they were restricted to analyzing the moderators at the between-study level and therefore do not account for any within-study variance.

Interestingly at the individual study level, significant age of onset effects, such that earlier age of onset is associated with poorer outcomes, were revealed for language function, [19, 67, 71] long-term storage and retrieval memory[39,76] processing speed [79] working memory and fluid intelligence.[13,41,68] These findings were not without contention, with other studies failing to find any significant age of onset related effects. [35,51,54,70] The disparity in findings between studies could, for example, be another possible explanation for why effects were not revealed at the study level.

Another limitation that warrants consideration is the overall moderate methodological quality of included studies. The available studies displayed several potential biases, including sampling, representativeness and reporting biases, which could have resulted in inaccurate estimation of effect sizes. Across most cognitive factors, overall NOS quality NOS ratings were not significantly related to the variability between studies. A single effect, approaching significance, showed that studies with higher methodological quality were associated with larger effect sizes for the *Gsm* factor. While it is possible that this finding represents a Type-I error due to the high number of analyses performed, it also highlights the need for better quality research in the study of this common condition. While it is acknowledged that there is variability in primary study goals and focus as well as the function of cognitive assessment, it is argued that the underlying quality factors including selection, comparability and exposure apply to every study such that any discrepancies in quality on the basis of study goal/focus may be a function of inadequate reporting rather than omission of the quality variables. Studies with sample sizes that were in the range of included studies were excluded on the basis of no control group. Therefore, the present meta-analysis is based on a smaller sample of published studies. It is noted that while normative data is critical for interpreting individual patient results, control samples grant a greater level of control over extraneous variables (e.g., demographic, testing environment, and cohort factors) in a clinical research context.

Future studies should ensure consistency in the measurement and reporting of disease variables, diagnostic criteria as well as sampling methods. Representativeness of sampling would be improved with consecutive recruitment. Given the nature of nocturnal semiology, researchers should be blinded to case or control status to reduce experimenter bias. Additionally, studies should carefully consider the impact of exclusion criteria which could otherwise impede the representativeness of study findings.

Further implications and future directions

Across a comprehensive range of different cognitive abilities, the standardized mean differences ranged between -0.50 and -0.81, in favor of healthy controls. In more clinically applicable terms, this difference corresponds to an approximate 7.5 to 12-point reduction in IQ for children with ECTS compared to their healthy peers on average, a non-trivial difference. Thus despite the observation of normal range standard scores at the group level, the "individual" is at a higher risk of experiencing cognitive difficulties compared to their healthy peers. We assert that research simply reporting that children with ECTS tend to have IQ's broadly in the "average" or "normal" range may be underestimating the real differences from their peers. It is also important to consider the substantial heterogeneity of effect sizes between studies for all cognitive factors. Thus, while children with ECTS are *more likely* to experience poorer cognitive outcomes, such high variability suggests that cognitive dysfunction is not unequivocal sequelae of the disease. As with normal individual differences, the cognitive profile of strengths and weaknesses in children with ECTS also appears to be variable. Beyond studies that aggregate patient outcomes, reports of individual ECTS patients clearly reveal the heterogeneity of cognitive difficulties.[80] As such, it is imperative that an increased risk of cognitive difficulties in general is recognized and monitored in these children. Importantly, this comprehensive synthesis of the data shows clinicians the effects of the condition are pervasive, even in light of recent revisions in conceptualization of effects

The scope of the current study was limited to investigating cognitive outcomes during the active epilepsy phase. A pertinent clinical question queries the presence of residual detriment in the recovery phase, that is, after seizure remission and

normalisation of the EEG. Although limited, several studies have explored the course of cognitive outcomes in ECTS through prospective longitudinal or retrospective follow-up designs, with mixed findings. A leading contention, at this stage, is that cognitive impairment in ECTS can, and often does, fully recover alongside epilepsy remission.[32,35,37,82] In addition, there is some evidence which indicates a greater likelihood for residual verbal/language-based deficits and poorer recovery that may be associated with greater severity and/or presence of atypical EEG features.[22,80] The tendency for residual *Gc* deficits perhaps resides from the greater likelihood of more pronounced cognitive disruption in this factor.

However, it is critical to consider that alike the research exploring cognitive outcomes in the active epilepsy phase, longitudinal studies are also methodologically limited, for example containing small sample sizes,[37] lack of control groups[22,80,82] and/or loss to follow up.[32,65] Thus, tentative conclusions may be drawn at this stage and a simple lack of statistically significant results in the scantiness of available studies could potentially lead to an underestimation of residual difficulties. More recently, Garcia-Ramos and colleagues[59] followed the trajectory of cognitive functioning in a cohort of children with new-onset ECTS over the first 2 years after diagnosis. They showed that cognitive development continued in cases and controls, however group differences remained stable overtime.[55] That is, children with ECTS continued to experience poorer cognitive outcomes relative to their healthy peers. Critically, only around half of the ECTS sample had achieved seizure remission at follow-up and EEG normalisation was not assessed.

More longitudinal research on cognitive outcomes beyond the active epilepsy phase is needed. In children with identified cognitive deficits, further studies exploring the efficacy of clinical interventions for minimizing the effects of poor cognition both during the active phase and for epilepsy remission, either non-pharmaceutical interventions or in conjunction with anti-epileptic therapy, are recommended. For example, Eom et al. (2016) piloted a 35-week exercise intervention with ten children with BECTS and revealed significant improvements in cognitive function and parental ratings of internalizing and behavioral problems as well as quality of life. This pilot data should be viewed with caution, given the small

sample size and absence of a comparison group but should encourage further controlled studies

Conclusions

The findings of the current study synthesize a somewhat disparate body of literature and challenge current models of specific or localized cognitive dysfunction in ECTS. Despite relatively larger effects seen for language based functions and memory encoding, all cognitive abilities displayed overlapping confidence intervals, with point estimates ranging from moderate-large deficits. As expected, substantial inconsistency and heterogeneity in effects was observed between studies across the different cognitive factors. In conclusion, children with ECTS display a profile of variable diffuse cognitive deficits, consistent with a model of widespread cortical dysfunction.

Key Points

- Children with ECTS show significantly poorer cognitive functioning relative to healthy controls, across all measured cognitive ability factors.
- While effect sizes varied, point estimates and associated confidence intervals indicated a profile of widespread and pervasive cognitive difficulties.
- Significant heterogeneity amongst studies suggested that sampling of patients with ECTS produces variable results.

References

1. Holmes GL. Benign focal epilepsies of childhood. Epilepsia 1993;34: 49-61.
2. Panayiotopoulos CP. Epileptic Syndromes and their Treatment. Springer Healthcare, Ltd., Manchester 2010.
3. Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, Hirsch E, Jain S, Mathern GW, Moshé SL, Nordli DR. ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017;58:512-21..
4. Gkampeta A, Pavlou E. Emerging genetic influences in benign epilepsy with centro-temporal spikes–BECTS. Epilepsy Res 2012;101:197-201.
5. Vadlamudi L, Kjeldsen MJ, Corey LA, et al. Analyzing the etiology of benign rolandic epilepsy: a multicenter twin collaboration. Epilepsia 2006;47:550-5.
6. Bouma PA, Bovenkerk AC, Westendorp RG, et al. The course of benign partial epilepsy of childhood with centrotemporal spikes A meta-analysis. Neurology 1997;48:430-7.
7. Vannest J, Tenney JR, Gelineau-Morel R, et al. Cognitive and behavioral outcomes in benign childhood epilepsy with centrotemporal spikes. Epilepsy Behav 2015;45:85-91.
8. Vinayan KP, Biji V, Thomas SV. Educational problems with underlying neuropsychological impairment are common in children with benign epilepsy of childhood with centrotemporal spikes (BECTS). Seizure. 2005;14:207-12.
9. Yung AW, Park YD, Cohen MJ, et al. Cognitive and behavioral problems in children with centrotemporal spikes. Pediatr Neurol 2000; 23:391-5.
10. Kim EH, Yum MS, Kim HW, et al. Attention-deficit/hyperactivity disorder and attention impairment in children with benign childhood epilepsy with centrotemporal spikes. Epilepsy Behav 2014;37:54-8.
11. Weglage J, Demsky A, Pietsch M, et al. Neuropsychological, intellectual, and behavioral findings in patients with centrotemporal spikes with and without seizures. Dev Med Child Neurol 1997;39:646-51.
12. *Xiao F, Lei D, An D, et al. Functional brain connectome and sensorimotor networks in rolandic epilepsy. Epilepsy Res 2015;113:113-25.

13. *Ayaz M, Karakaya I, Ayaz AB, et al. Psychiatric and Neurocognitive Evaluation Focused on Frontal Lobe Functions in Rolandic Epilepsy. Arc Neuropsychiatr 2013;50:209-15.
14. *Taner Y, Erdogan-Bakar E, Turanli, et al. Psychiatric evaluation of children with CSWS (continuous spikes and waves during slow sleep) and BRE (benign childhood epilepsy with centrotemporal spikes/rolandic epilepsy) compared to children with absence epilepsy and healthy controls. Turk J Pediatr 2007;49:397.
15. Connolly AM, Northcott E, Cairns DR, et al. Quality of life of children with benign rolandic epilepsy. Pediatr Neurol 2006; 35:240-5.
16. Verrotti A, Filippini M, Matricardi S, et al. Memory impairment and Benign Epilepsy with centrotemporal spike (BECTS): a growing suspicion. Brain Cog 2014; 84:123-31.
17. Kavros PM, Clarke T, Strug LJ, et al. Attention impairment in rolandic epilepsy: systematic review. Epilepsia 2008;49:1570-80.
18. Nicolai J, Aldenkamp AP, Arends J, et al. Cognitive and behavioral effects of nocturnal epileptiform discharges in children with benign childhood epilepsy with centrotemporal spikes. Epilepsy Behav 2006;8:56-70.
19. *Jurkevičienė G, Endzinienė M, Laukienė I, et al. Association of language dysfunction and age of onset of benign epilepsy with centrotemporal spikes in children. Euro J Paediatr Neurol 2012;16:653-61
20. * Lillywhite LM, Saling MM, Harvey SA, et al. Neuropsychological and functional MRI studies provide converging evidence of anterior language dysfunction in BECTS. Epilepsia 2009; 50:2276-84.
21. Smith AB, Bajomo O, Pal DK. A meta-analysis of literacy and language in children with rolandic epilepsy. Dev Med Child Neurol 2015;57:1019-26.
22. Filippini M, Boni A, Giannotta M, et al. Neuropsychological development in children belonging to BECTS spectrum: long-term effect of epileptiform activity. Epilepsy Behav 2013;28:504-11.
23. Aldenkamp AP., Arends J. Effects of epileptiform EEG discharges on cognitive function: is the concept of “transient cognitive impairment” still valid?. Epilepsy Behav 2004; 5: 25-34.

24. McGrew KS. CHC theory and the human cognitive abilities project: Standing on the shoulders of the giants of psychometric intelligence research. Intelligence 2009; 1-10.
25. Floyd RG, Bergeron R. Hamilton G. & Parra GR. How do executive functions fit with the Cattell-Horn-Carroll model? Some evidence from a joint factor analysis of the Delis-Kaplan executive function system and the Woodcock-Johnson III tests of cognitive abilities. Psychol Sch 2010; 47: 721-738.
26. Larrabee GJ. Association between IQ and neuropsychological test performance: Commentary on Tremont, Hoffman, Scott, and Adams 1998. Clin Neuropsychol 2000; 14: 139-145.
27. Loring DW, & Larrabee GJ. Sensitivity of the Halstead and Wechsler Test Batteries to brain damage: Evidence from Reitan's original validation sample. The Clin Neuropsychol 2006; 20: 221–229.
28. Loughman A, Bowden SC, D'souza W. Cognitive functioning in idiopathic generalised epilepsies: A systematic review and meta-analysis. Neuro Biobehav Rev 2014; 43:20-34.
29. Jewsbury PA, Bowden SC. Construct Validity of Fluency and Implications for the Factorial Structure of Memory. J Psychoedul Assess 2016: 1-22.
30. Jewsbury PA, Bowden SC, Strauss ME. Integrating the switching, inhibition, and updating model of executive function with the Cattell—Horn—Carroll model. J Experi Psy 2015: 1-25.
31. Moher D, Liberati A, Tetzlaff J, et al. Prisma Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS med 2009;6.
32. *D'Alessandro P, Piccirilli M, Tiacci C, et al. Neuropsychological features of benign partial epilepsy in children. Ital J Neurol Sci 1990;11:265-9.
33. *Piccirilli M, D'Alessandro P, Sciarma T, et al. Attention problems in epilepsy: possible significance of the epileptogenic focus. Epilepsia 1994;35:1091-6.
34. *Riva D, Vago C, Franceschetti S, et al. Intellectual and language findings and their relationship to EEG characteristics in benign childhood epilepsy with centrotemporal spikes. Epilepsy Behav 2007;10:278-85

35. * Verrotti A, D'Egidio C, Agostinelli S, et al. Cognitive and linguistic abnormalities in benign childhood epilepsy with centrotemporal spikes. Acta Paediatrica. 2011;100:768-72.
36. *Zhu Y, Yu Y, Shinkareva SV, et al. Intrinsic brain activity as a diagnostic biomarker in children with benign epilepsy with centrotemporal spikes. Hum Brain Map 2015;36:3878-89.
37. *Baglietto MG, Battaglia FM, Nobili L, et al. Neuropsychological disorders related to interictal epileptic discharges during sleep in benign epilepsy of childhood with centrotemporal or Rolandic spikes. Dev Med Child Neurol 2001;43:407-12.
38. *Tzitiridou M, Panou T, Ramantani G, et al. Oxcarbazepine monotherapy in benign childhood epilepsy with centrotemporal spikes: a clinical and cognitive evaluation. Epilepsy Behav 2005;7:458-67.
39. *Vago C, Bulgheroni S, Franceschetti S, et al. Memory performance on the California Verbal Learning Test of children with benign childhood epilepsy with centrotemporal spikes. Epilepsy Behav 2008;13:600-6.
40. *Lopes AF, Simões MR, Monteiro JP, et al.. Intellectual functioning in children with epilepsy: Frontal lobe epilepsy, childhood absence epilepsy and benign epilepsy with centro-temporal spikes. Seizure 2013;22:886-92.
41. *Lopes AF, Monteiro JP, Fonseca MJ, et al. Memory functioning in children with epilepsy: frontal lobe epilepsy, childhood absence epilepsy, and benign epilepsy with centrotemporal spikes. Behav Neurol 2014
42. Newton JH, McGrew KS. Introduction to the special issue: Current research in Cattell–Horn–Carroll–based assessment. Psych Schools. 2010;47:621-34.
43. Borenstein M, Hedges L, Higgins J, et al. Comprehensive meta analysis [computer program]. Englewood, NJ: Biostat 2000.
44. Borenstein M, Hedges LV, Higgins J, et al. Introduction to meta-analysis. John Wiley & Sons, Ltd; 2009.
45. Cohen J. The earth is round (p<. 05). 1994 Rejoinder.
46. Sanderson S, Tatt ID, Higgins JP. Tools for assessing quality and susceptibility to bias in observational studies in epidemiology: a systematic review and annotated bibliography. Intern J Epidem 2007;36:666-76.

47. Wells GA, Shea B, O'connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Available at: h ttp. ohri. ca/programs/clinical_epidemiology/oxford. asp (accessed June 2014). 2008.
48. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Euro J Epidem 2010;25:603-5.
49. *Boscariol M, Casali RL, Amaral MI, et al. Language and central temporal auditory processing in childhood epilepsies. Epilepsy Behav 2015;53:180-3.
50. *Völkl-Kernstock S, Willinger U, Feucht M. Spacial perception and spatial memory in children with benign childhood epilepsy with centro-temporal spikes (BCECTS). Epilepsy Res 2006;72:39-48.
51. *Völkl-Kernstock S, Bauch-Prater S, Ponocny-Seliger E, et al. Speech and school performance in children with benign partial epilepsy with centro-temporal spikes (BCECTS). Seizure 2009;18:320-6.
52. *Ayaz M, Kara B, Soylu N, et al. Fine motor skills in children with rolandic epilepsy. Epilepsy Behav 2013;29:322-5.
53. *Boatman DF, Trescher WH, Smith C, et al. Cortical auditory dysfunction in benign rolandic epilepsy. Epilepsia 2008;49:1018-26.
54. *Cerminara C, D'Agati E, Lange KW, et al.. Benign childhood epilepsy with centrotemporal spikes and the multicomponent model of attention: a matched control study. Epilepsy Behav 2010;19:69-77.
55. *Ciumas C, Saignavongs M, Ilski F, et al. White matter development in children with benign childhood epilepsy with centro-temporal spikes Brain. 2014.
56. *Croona C, Kihlgren M, Lundberg S, et al. Neuropsychological findings in children with benign childhood epilepsy with centrotemporal spikes. Dev Med Child Neurol 1999;41:813-8.
57. *Datta AN, Oser N, Bauder F. et al, Cognitive impairment and cortical reorganization in children with benign epilepsy with centrotemporal spikes. Epilepsia 2013;54:487-94.

58. *Filippini M, Ardu E, Stefanelli S, et al. Neuropsychological profile in new-onset benign epilepsy with centrotemporal spikes (BECTS): Focusing on executive functions. Epilepsy Behav. 2016;54:71-9.
59. *Garcia-Ramos C, Jackson DC, Lin JJ, et al. Stafstrom CE, Zawadzki L, Seidenberg M, Prabhakaran V, Hermann BP. Cognition and brain development in children with benign epilepsy with centrotemporal spikes. Epilepsia 2015;56:1615-22.
60. *Genizi J, Shamay-Tsoory SG, Shahar E, et al. Impaired social behavior in children with benign childhood epilepsy with centrotemporal spikes. J Child Neurol 2012;27:156-61.
61. *Heijbel J, Bohman M. Benign epilepsy of children with centrotemporal EEG foci: intelligence, behavior, and school adjustment. Epilepsia 1975;16:679-87.
62. *Jackson DC, Dabbs K, Walker NM, et al. The neuropsychological and academic substrate of new/recent-onset epilepsies. J Pediatr 2013;162:1047-53.
63. *Kárpáti J, Donauer N, Somogyi E, et al. Working Memory Integration Processes in Benign Childhood Epilepsy with Centrotemporal Spikes. Cog Behav Neurol 2015;28:207-14.
64. *Kim SE, Lee JH, Chung HK, et al. Alterations in white matter microstructures and cognitive dysfunctions in benign childhood epilepsy with centrotemporal spikes. Euro J Neurol 2014;21:708-17.
65. Lindgren Å, Kihlgren M, Melin L, et al. Development of cognitive functions in children with rolandic epilepsy. Epilepsy Behav 2004;5:903-10.
66. *Luo C, Zhang Y, Cao W, et al. Altered structural and functional feature of striato-cortical circuit in benign epilepsy with centrotemporal spikes. Intern J Neur Sys 2015: 1-13.
67. *Ma Y, Chen G, Wang Y, et al. Language dysfunction is associated with age of onset of benign epilepsy with centrotemporal spikes in children. Euro Neurol 2015;7:179-83.
68. *Neri ML, Guimarães CA, Oliveira EP, et al. Neuropsychological assessment of children with rolandic epilepsy: executive functions. Epilepsy Behav 2012;24:403-7.

69. *Northcott E, Connolly AM, Berroya A, et al. Memory and phonological awareness in children with Benign Rolandic Epilepsy compared to a matched control group. Epilepsy Res 2007;75:57-62.
70. *Overvliet GM, Besseling RM, van der Kruijs SJ, et al. Clinical evaluation of language fundamentals in Rolandic epilepsy, an assessment with CELF-4. Euro J Paediat Neurol 2013;17:390-6.
71. *Piccinelli P, Borgatti R, Aldini A, et al. Academic performance in children with rolandic epilepsy. Dev Med Child Neurol 2008;50:353-6.
72. *Smith AB, Kavros PM, Clarke T, et al. neurocognitive endophenotype associated with rolandic epilepsy. Epilepsia 2012;53:705-11.
73. *Vannest J, Szaflarski JP, Eaton KP, et al. Holland SK. Functional magnetic resonance imaging reveals changes in language localization in children with benign childhood epilepsy with centrotemporal spikes. J Child Neurol 2013;28:435-45.
74. *Vannest J, Tenney JR, Altaye M, et al. Impact of frequency and lateralization of interictal discharges on neuropsychological and fine motor status in children with benign epilepsy with centrotemporal spikes. Epilepsia. 2016;57: 161-67.
75. *Verrotti A, Matricardi S, Di Giacomo D, et al. Neuropsychological impairment in children with Rolandic epilepsy and in their siblings. Epilepsy Behav 2013;28:108-12.
76. *Vintan MA, Palade S, Cristea A, et al. A neuropsychological assessment, using computerized battery tests (CANTAB), in children with benign rolandic epilepsy before AED therapy. J Med Life 2012;5:114.
77. Rzezak P, Valente KD, Duchowny MS. Temporal lobe epilepsy in children: executive and mnestic impairments. Epilepsy Behav 2014;31:117-22.
78. *Wu Y, Ji GJ, Zang YF, Liao W, et al. Local activity and causal connectivity in children with benign epilepsy with centrotemporal spikes. PloS one 2015;10:e0134361.
79. *Yang B, Wang X, Shen L, et al. The attentional networks in benign epilepsy with centrotemporal spikes. Epilepsy Behav. 2015;53:78-82.
80. Massa R, de Saint–Martin A, Carcangiu R, et al. EEG criteria predictive of complicated evolution in idiopathic rolandic epilepsy. Neurology 2001;57:1071-9.

81. Bressler SL, Menon V. Large-scale brain networks in cognition: emerging methods and principles. Trends Cog Sci 2010;14:277-90.
82. Deonna T, Zesiger P, Davidoff V, et al. Benign partial epilepsy of childhood: a longitudinal neuropsychological and EEG study of cognitive function. Dev Med Child Neurol 2000;42:595-603.
83. Eom S, Lee MK, Park JH, et al. The Impact of a 35-Week Long-Term Exercise Therapy on Psychosocial Health of Children With Benign Epilepsy. J Child Neurol 2016;31:985-90.

Disclosure of Conflicts of Interest

None of the authors has any conflict of interest to disclose.

Ethical Publication Statement

We confirm that we have read the Journals position on issues involved in ethical publication and affirm that this report is consistent with those guidelines

Tables titles:

Table 1. *Cattell-Horn-Carroll Model Factors (adapted from Newton & McGrew, 2010; Jewsbury & Bowden, 2016).*

Table 2. *Characteristics of Included Studies*

Table 3. *Summary Table of Meta-Analyses for each CHC factor*

Figures Titles:

Figure 1. Prisma flow diagram of eligibility screening of studies

Table 1.

Cattell-Horn-Carroll Model Factors (adapted from Newton & McGrew, 2010; Jewsbury & Bowden, 2016).

Cognitive Factor	Description
G	An overarching factor of general intellectual function
Gc – Acquired Knowledge	The knowledge of the culture that is incorporated by individual's vis-a-vis a process of acculturation. Gc is typically described as a person's breadth and depth of acquired knowledge of the language, information, and concepts of a specific culture and/or the application of this knowledge. Gc is primarily a store of verbal or language-based declarative (knowing what) and procedural (knowing how) knowledge acquired through the investment of other abilities during formal and informal educational and general life experiences. Historically it is often referred to as crystallized intelligence.
Gf – Fluid reasoning	The use of deliberate and controlled mental operations, often in a flexible manner, to solve novel problems that cannot be performed automatically. Mental operations often include drawing inferences, concept formation, classification, generalization, generating and testing hypothesis, identifying relations, comprehending implications, problem solving, extrapolating, and transforming information. Inductive and deductive reasoning are generally considered the hallmark indicators of Gf. Historically is often referred to as fluid intelligence.
Gsm – Short-term Memory	The ability to apprehend and maintain awareness of a limited number of elements of information in the immediate situation. A limited-capacity system that loses information quickly through the decay of memory traces, unless an individual activates other cognitive resources to maintain the information in immediate awareness.
Gs – Processing Speed	The ability to automatically and fluently perform relatively easy or overlearned elementary cognitive tasks, especially when high mental efficiency (i.e., attention and focused concentration) is required.
Gv – Visual Processing	The ability to generate, store, retrieve, and transform visual images and sensations. Gv abilities are typically measured by tasks (viz., figural or geometric stimuli) that require the perception and transformation of visual shapes, forms, images, and/or tasks that require maintaining spatial

	orientation with regard to objects that may change or move through space.
Glr – Long-term Storage and Retrieval	The ability to store and consolidate new information in long-term memory and later fluently retrieve the stored information (e.g., concepts, ideas, items, names) through association. Memory consolidation and retrieval can be measured in terms of information stored for minutes, hours, weeks, or longer. Some Glr narrow abilities have been prominent in creativity research (e.g., production, ideational fluency, or associative fluency).
Gf – Fluency-retrieval	The ability to retrieve information from long-term storage. Gr is composed of narrow abilities related to orthographic, semantic word and semantic prose fluency ability. This factor is thought to primarily reflect retrieval abilities independent of information encoding.

Table 2. Characteristics of Included Studies

Study	Overall NOS Quality Rating	n (pt)	n (con)	Age (pt)	Age of onset	AED use	EEG foci			ILAE	Exclusion Criteria	
							R	L	B		IQ	Psychiatric Disorder
Ayaz et al. (2013)[52]	5	31	31	10.17	8.1	24/31	12	10	9	Y	<70	N
Ayaz et al. (2013)[13]	5	44	44	10.05	7.9	44/44	18	15	11	Y	<70	N
Baglietto et al.. (2001)[37]	6	9	9	9.12	7.9	9/9	4	5		N/R	N/R	N
Boatman et al (2008)[53]	5	7	7	10.07	7.25	nil	1	4	1	N/R	<90	Y
Boscariol et al (2015)[49]	3	12	16	11.56	4.17	N/R		N/R		Y	<80	N
Cerminara et al., (2010)[54]	7	21	21	9.86	3-12	nil	11	10		Y	<85	Y
Ciumas et al., (2014)[55]	5	25	25	9.6	7.5	10/25	14	2	5	Y	N/R	N
Croona et al. (1999)[56]	6	17	17	12.5	5.5	12/17		N/R		N/R	N/R	Y
D'Alessandro et al. (1990)[32]	4	44	9	10.7	5-9	Nil	11	18	15	N/R	<80	N
Datta et al. (2013)[57]	3	27	19	9.9	7.9	15/27	15	9	4	N/R	N/R	N
Filippini et al. (2016)[58]	5	15	15	8.8	-	Nil	5	2	8	Y	<80	M
Garcia-Ramos et al. (2015)[59]	6	24	41	10.5	1.7	15/24		N/R		Y	<70	N
Genizi et al. (2012)[60]	8	15	15	10.5	7.6	14/15	-	-	15	N/R	N/R	Y

Heijbel, J., Bohman, M. (1975)[61]	5	16	16	8.9	6.1	13/16	-	3	13	N/R	N/R	N
Jackson et al. (2013)[62]	5	22	72	10.25	9	14/22		N/R		N/R	N/R	N
Jurkevičienė et al. (2012)[19]	5	61	35	9.5	7.8	31/61	20	22	12	N/R	<70	Y
Kárpáti et al. (2015)[63]	7	17	17	9.02	3-13	13/17	5	4	8	Y	N/R	Y
Kim et al. (2014)[64]	7	19	25	10.7	N/R	14/19	4	6	10	Y	<60	Y
Lillywhite et al. (2009)[20]	6	20	20	9.2	N/R	10/20	7	8	5	N/R	N/R	N
Lopes et al. (2013)[40] & Lopes et al. (2014)[41]	5	30	30	9.8	6.77	22/30		N/R		Y	<70	N
Luo et al. (2015)[66]	6	21	20	9.12	8.02	9/21	4	7	10	Y	N/R	Y
Ma et al. (2015)[67]	8	63	30	9.57	9.6	41/63	24	28	11	N/R	<70	Y
Neri et al. (2012)[68]	6	25	28	10.9	5.7	17/25	7	7	11	Y	<80	Y
Northcott et al. (2007)[69]	5	42	40	8.5	N/R	27/42		N/R		Y	N/R	N
Overvliet et al. (2013)[70]	1	25	25	11.3	7.8	17/25		N/R		N/R	<70	Y
Piccinelli et al. (2013)[71]	8	20	21	10.25	7.8	15/20	6	7	6	Y	N/R	N

Piccirilli et al. (1994)[33]	6	43	15	10.8	N/R	nil	14	14	15	N/R	<80	N
Riva et al. (2007)[34] & Vago et al. (2008)[39]	7	24	16	9.4	7	5/24	16	8	-	N/R	<80	Y
Smith et al. (2012)[72]	4	13	11	10.83	7.54	6/13	1	3	9	N/R	N/R	N
Taner et al. (2007)[14]	4	42	40	9.85	N/R	Nil		N/R		N/R	N/R	N
Tzitiridou et al (2005)[38]	6	70	45	8.4	8.4	Nil		N/R	-	Y	N/R	N
Vannest et al. (2013)[73]	2	15	15	8.53	8.13	6/15	6	7	1	N/R	N/R	Y
Vannest et al. (2016)[74]	3	34	48	7.94	7.94	Nil	18	8	8	N/R	N/R	N
Verrotti et al. (2011)[35]	7		12							Y	<80	N
No AED Subgroup		10		9.6	9.6	Nil	4	2	4			
AED Subgroup		15		7.8-11.3	9.5	15/15	6	6	3			
Verrotti et al. (2013)[75]	9	9	18	7.8	7.8	Nil	2	4	3	N/R	N/R	N
Vinţan et al. (2012)[76]	5	18	18	8.88	6.97	nil	5	13	-	Y	N/R	N
Völkl-Kernstock et al. (2006)[50]	8	22	22	8-9	N/R	6/22	12	8	-	Y	<85	N
Volkl-Kernstock et al. (2009)[51]	7	20	20	6-14.1	N/R	12/20	6	5	9	Y	<85	N

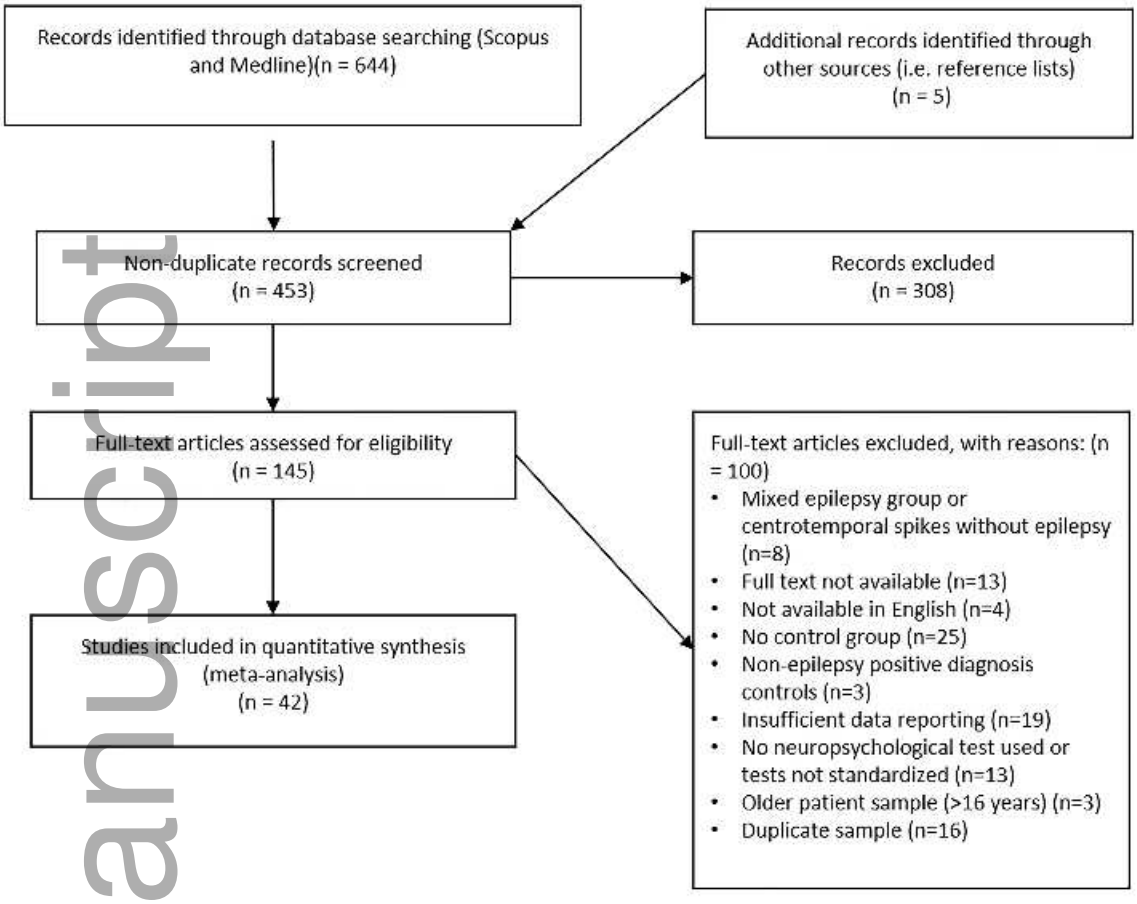
Wu et al. (2015)[77]	3	24	18	9.8	N/R	nil		N/R		Y	<70	Y
Xiao et al. (2015)[78]	2	73	73	9.7	N/R	30/73	33	30	10	Y	<75	Y
Yang et al. (2015)[79]	6	90	90	8.47	7.09	nil	34	32	21	Y	N/R	N
Zhu et al. (2015)[36]	5									Y	<70	N
IED subgroup		20	28	9	6.95	11/20	13	6	1			
Non-IED subgroup		23	28	10.22	7.48	17/23	11	10	2			

Note: NOS quality rating = Total Newcastle-Ottawa: quality rating , Y = Yes, N = No, N/R = Not-reported, n (pt) = total number of BECTS children in study, n (con) = total number of control children in study, Age (pt) = mean age of BECTS children at testing, Age of onset = mean age of seizure/epilepsy onset for BECTS children, AED use = number of BECTS children on anti-epileptic drug, EEG foci = location of predominant electroencephalographic CTS, R = Right hemisphere, L = Left hemisphere, B = Bilateral, ILAE = explicit reference to International League Against Epilepsy diagnostic criteria, IQ exclusion = patient exclusion from study based on Intelligence Quotient, Psychiatric Disorder exclusion = patient exclusion from study based on presence of psychiatric or developmental disorder.

Table 3. Summary Table of Meta-Analyses for each CHC factor

CHC Factor	K	N	SMD	CI -	CI +	(df) Q	I^2	Tau^2
G	27	812	-0.62	-0.83	-0.41	(26) 106.79*	75.65	0.22
Gc	29	890	-0.79	-1.00	-0.57	(28) 120.17*	76.70	0.25
Gf	27	763	-0.54	-0.74	-0.33	(26) 94.17*	72.39	0.20
Gsm	18	483	-0.52	-0.80	-0.24	(17) 67.26*	74.73	0.26
Gs	22	744	-0.60	-0.85	-0.34	(21) 106.91*	80.36	0.28
Gv	12	312	-0.42	-0.72	-0.13	(11) 31.29*	64.84	0.16
Glr	12	277	-0.81	-1.13	-0.48	(11) 33.76*	67.20	0.21
Gr	10	298	-0.79	-1.18	-0.40	(9) 39.42*	77.17	0.29

Note: K = number of studies, N = number of children with BECTS, SMD – Standardised Mean Difference, CI- = lower 95% confidence interval, CI+ = upper 95% confidence, * = p<.001



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