Quantifying the deficit—imaging neurobehavioural impairment in childhood epilepsy

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Background: Neurobehavioral impairments such as learning difficulty, autism, attention deficit hyperactivity disorder (ADHD) and mood or behavioural problems are known to be increased in children with epilepsy; however, they remain under-recognised and often cause considerable morbidity. Quantitative neuroimaging techniques offer a potential avenue to improving our understanding of the underlying pathological basis for these disorders, aiding with diagnosis and risk stratification.

Methods: A systematic review was undertaken for original research articles involving magnetic resonance imaging in children with epilepsy and one or more neurobehavioural impairments. Studies were reviewed with respect to patient population, methodology and magnetic resonance imaging (MRI) findings.

Results: A total of 25 studies were identified and included in this review. The majority of studies looked at single impairments, commonly cognitive impairment or ADHD, with few studies reporting on other impairments. Reductions in cortical grey matter and disruptions of functional and structural brain networks were associated with poorer cognitive performance and disruptions of grey and white matter within a fronto-striatal-cerebellar network associated with ADHD. Insufficient studies were available to report on other impairments.

Conclusions: Relatively few studies exist in this field and those that do are methodologically diverse. Further investigation is required to determine if the changes reported to date are epilepsy syndrome specific or have broader applicability.

Keywords: Epilepsy; comorbidity; neurobehavioural impairment; autism; attention deficit hyperactivity disorder (ADHD); depression; cognitive impairment

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Introduction

It is acknowledged that there is a high incidence of neurobehavioural disorders in children with epilepsy (1) and that these associated cognitive, behavioural and psychological impairments can be equally, if not more disabling than the epileptic seizures themselves. Studies of quality of life and long term social outcomes in children with epilepsy have shown that the presence and severity of neurobehavioural impairments is a stronger predictor of long term outcome than seizure control or other epilepsy related factors (2,3). Nevertheless they remain an often overlooked part of epilepsy management (4,5).

There is now an extensive literature showing that the incidence of several neuropsychiatric/neurobehavioural disorders, including depression (6), learning disability (LD) (7), attention deficit hyperactivity disorder (ADHD) (8) and autistic spectrum disorder (ASD) (9) is significantly increased in children with epilepsy over and above that seen in healthy children or children with other childhood illnesses such as migraine, diabetes or asthma (5,10-13). However, our understanding of the underlying neurological basis
for this association remains in its infancy. Many of these impairments have been shown to be present at or pre-date seizure onset (14-17), moreover, the relationship between epilepsy-related factors such as seizure control, treatment or epilepsy syndrome and neurobehavioural impairments is not straightforward (12,18-21). One conclusion from this is that, while seizures may play a role, they are unlikely to be the only pathological factor and attention needs to be focused on underlying abnormalities that may be responsible for both the impairment and the epilepsy together.

The majority of children with epilepsy, including those with neurobehavioural impairments, do not have visible abnormalities on neuroimaging (22). While improvements in imaging technology may allow the visualisation of hitherto undetected macroscopic abnormalities (23) this will still remain a minority of patients. The use of advanced neuroimaging techniques such as automated cortical thickness/volume measurements, functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI) has the ability to provide information on changes to brain microstructure, connectivity and organisation over and above that available from conventional imaging and there are now a number of studies showing that children with epilepsy show subtle differences in grey matter volumes, white matter integrity and network connectivity compared to healthy control groups (24). There is growing interest in relating these concepts to neurobehavioural impairments in children with epilepsy and it is hoped that this may provide further insight into the neurological basis of these impairments and their underlying causes. By understanding the “neural signature” of these conditions it may then be possible to identify biomarkers to assist with early diagnosis and risk stratification.

One barrier is that quantitative magnetic resonance imaging (MRI) techniques, including volumetry, cortical thickness measurements, DTI, fMRI or structural/functional network analysis (Figure 1) have rarely been systematically applied in children with epilepsy. Furthermore, those studies that have been carried out have tended to focus on specific subtypes of epilepsy and specific neurobehavioural impairments. Since there is a tendency for impairments to cluster and frequently occur in association with one another there is a need to consider the evidence in toto to identify common factors. The purpose of this review is to try and draw together the disparate threads of evidence from studies looking at different impairments and comorbidities to assess the utility of different quantitative MRI techniques to detect and understand their common foundation.

Figure 1 Quantitative MRI analysis techniques. (A) Subcortical volumetry (B) tract-bract-based spatial statistics (C) graph network analysis (D) cortical thickness measurements (E) tractography.
Methods

Articles relevant to this review were identified by searches of the PubMed (National Center for Biotechnology Information), Medline/OvidSP, Web-of-Science and BIOSIS databases, performed on 17th August 2014. Medical Subject Heading (MeSH) terms “Epilepsy” (including all sub-categories) and “MR”, “diffusion tensor imaging”, “diffusion magnetic resonance imaging”, “neuroimaging” were combined with appropriate terms for different specific impairments as follows:

(I) “attention deficit hyperactivity disorder”, “attention deficit disorder”, “attention deficit disorder with hyperactivity”;


(III) “cognition”, “cognitive disorders”, “learning difficulty”, “mental retardation”, “intellectual impairment”;

(IV) “behavioural problems”, “personality disorder”, “oppositional defiant disorder”;

(V) “mood disorders”, “anxiety”, “depression”;

(VI) “neurobehavioural impairment”, “comorbidity”, “neurodevelopmental impairment”, “neuropsychological impairment”.

Searches were limited to original research studies in English involving children under the age of 18. In addition references from relevant original articles and review articles were added if not identified from these searches. The titles and abstracts of all articles identified from these searches and where necessary to make a decision on inclusion, the full text article were retrieved and reviewed. Criteria applied for consideration of inclusion in this review were that the article should have reported on the results of an original research study involving neuroimaging in patients with epilepsy and one of the above-mentioned impairments with comparison to a suitable control group, and that the study should include a group of children under the age of 18 years and report separately on this group. Studies with a mixed group of children and adults were not included unless there was a separate analysis only including the child group. Studies that focused exclusively on children post-epilepsy surgery were excluded.

Results

From the initial search 2,746 articles were identified. Of these 24 were considered applicable to this review. The majority of the excluded articles either did not address MRI or neurobehavioural findings, contained only single case reports or reviews of existing data, did not report neuroimaging in a systematic way or only included children with epilepsy incidentally and did not report on them as a specific group. Figure 2 shows how the identified articles were categorised by type of impairment. One additional article was identified from references and is described below.

Attention deficit hyperactivity disorder (ADHD)

Five articles investigating ADHD in children with epilepsy...
Autism

No systematic neuroimaging studies involving patients with autism and epilepsy were identified. A number of studies described MRI findings in patients with tuberous sclerosis (with and without epilepsy) suggesting that the type and location of tubers might be linked with the risk of epilepsy and autistic behaviour (32-34), but none of these included a control group and they did not elaborate on any link between the autism and the epilepsy. All other studies either did not review any neuroimaging or presented isolated case reports.

The suggestion has been made that the increased risk of autism in children with epilepsy can be mainly explained by the increased incidence of learning difficulty rather than being linked to the epilepsy itself (9,35). Currently little evidence exists to refute this hypothesis, although the association of autism with specific epilepsy syndromes such as infantile spasms does suggest that there may still be specific mechanisms at work.

Cognition

There were 15 articles identified that investigated the relationship between one or more aspects of cognition, epilepsy and brain structure. These articles covered a number of different epilepsy syndromes and investigated a number of different cognitive aspects and are therefore difficult to compare directly. Findings are summarised in Table 2.

The most common types of epilepsy to be studied were benign epilepsy with centro-temporal spikes (BECTS), childhood absence epilepsy (CAE) and idiopathic epilepsy with complex partial seizures (CPS). The majority of studies, apart from one early study by Lawson et al. (36), used validated neuropsychological tests to assess cognitive function. The main assessment tools used were the WISC-III (37) for general cognition/intelligence and the Delis-Kaplan Executive Function System (38) for executive function, with single studies using other tools such as the Test of Language Development (39) and the Children’s Memory Scale (40). MRI investigations were more heterogeneous, with a number of different structural and functional imaging techniques used and little overlap between individual studies.

In general abnormal structural neuroimaging (41,42) and, in particular, a loss of cortical grey matter volume (43-47) was associated with poorer cognitive performance/cognitive impairment. There is however little agreement...
<table>
<thead>
<tr>
<th>Study</th>
<th>Epilepsy type</th>
<th>Imaging modality</th>
<th>Age (year)</th>
<th>Number</th>
<th>Significant exclusions</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bechtel et al. 2012 free for &gt;6 months</td>
<td>Unspecified, seizure free for &gt;6 months</td>
<td>fMRI</td>
<td>8-14</td>
<td>17 boys with EP+ADHD, 15 boys with ADHD, 15 healthy controls</td>
<td>IQ &lt;70, other developmental or neurological disorder, abnormal MRI</td>
<td>EP + ADHD group showed similar problems to pure ADHD group with working memory and reduced activation in frontal, parietal, right thalamus and medial/lateral cerebellum compared to controls</td>
</tr>
<tr>
<td>Cohen et al. 2009 childhood absence epilepsy</td>
<td>Childhood absence epilepsy</td>
<td>Structural MRI</td>
<td>6.6-15</td>
<td>26 children with CAE, 8 of whom had ADHD; 26 healthy controls</td>
<td>Other seizure types, no seizures in past year, other neurological disorders</td>
<td>Bilateral reduced thalamic volumes in children with CAE and ADHD compared to those with CAE without ADHD</td>
</tr>
<tr>
<td>Bechtel et al. 2009 BECTS and atypical absence seizures</td>
<td>Frontal lobe epilepsy, BECTS and atypical absence seizures</td>
<td>DTI</td>
<td>9-14</td>
<td>8 boys with EP+ADHD, 14 boys with ADHD, 12 healthy controls</td>
<td>IQ &lt;70, other developmental or neurological disorder, abnormal MRI</td>
<td>Both children with Epilepsy + ADHD and children with developmental ADHD showed reduced FA in the cerebellum</td>
</tr>
<tr>
<td>Hermann et al. 2007 idiopathic epilepsy</td>
<td>Idiopathic epilepsy</td>
<td>Structural MRI</td>
<td>8-18</td>
<td>72 children with new-onset epilepsy, 23 of whom had ADHD; 63 healthy first-degree cousins</td>
<td>Other developmental or neurological disorder, abnormal MRI, abnormal neurological examination</td>
<td>Increased frontal lobe grey matter volume and decreased total brainstem volume in children with EP+ADHD compared to children with EP-ADHD and healthy controls</td>
</tr>
</tbody>
</table>

Abbreviations: BECTS, benign epilepsy with centro-temporal spikes; CAE, childhood absence epilepsy; EP, epilepsy (+/- ADHD); ADHD, attention deficit hyperactivity disorder; MRI, magnetic resonance imaging; fMRI, functional magnetic resonance imaging; DTI, diffusion tensor imaging; FA, fractional anisotropy.
Table 2 MRI studies of cognitive impairment in children with epilepsy

<table>
<thead>
<tr>
<th>Study</th>
<th>Imaging modality</th>
<th>Age (year)</th>
<th>Number</th>
<th>Epilepsy type</th>
<th>Significant exclusions</th>
<th>Neuropsychological measurements</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bonilha et al. 2014</td>
<td>Structural network analysis based on cortical thickness</td>
<td>8-18</td>
<td>39 patients, 28 healthy controls</td>
<td>New onset epilepsy</td>
<td>Abnormal clinical MRI, diagnosed with epilepsy &gt;12 months previously</td>
<td>WISC-III, D-KEFS</td>
<td>Patients with lower IQ and greater executive dysfunction showed reduced network efficiency and resilience</td>
</tr>
<tr>
<td>Vaessen et al. 2014</td>
<td>fMRI and DTI based network analyses</td>
<td>8-13</td>
<td>26 patients, 36 healthy controls</td>
<td>FLE</td>
<td>Abnormal clinical MRI, other neurological problem, history of cognitive problems</td>
<td>Computerised visual searching task</td>
<td>Increased functional modularity score associated with worse performance on cognitive task</td>
</tr>
<tr>
<td>Widjaja et al. 2013</td>
<td>DTI</td>
<td>7-17</td>
<td>40 patients, 25 healthy controls</td>
<td>Focal seizures being investigated for possible epilepsy surgery</td>
<td>Abnormal clinical MRI</td>
<td>WISC-III, D-KEFS CMS</td>
<td>Reduced right temporal FA in patients correlates to impaired language and executive function performance. Reduced corpus callosum FA correlates to impairments of language and IQ</td>
</tr>
<tr>
<td>Datta et al. 2013</td>
<td>fMRI</td>
<td>7-13</td>
<td>27 patients, 19 controls</td>
<td>BECTS</td>
<td>Abnormal clinical MRI, other neurological disorder</td>
<td>WISC-III</td>
<td>Bilateral activation of inferior frontal gyrus and supplementary motor area in patients vs. left sided activation in controls during language tasks</td>
</tr>
<tr>
<td>Braakman et al. 2013</td>
<td>DTI</td>
<td>8-13</td>
<td>37 patients, 42 controls</td>
<td>FLE</td>
<td>Abnormal clinical MRI, history of brain trauma, other neurological disorder</td>
<td>WISC-III</td>
<td>Patients with FLE and cognitive impairment showed increased FA in bilateral occipital lobes and decreased FA/tract volume in frontal white matter tract bundles</td>
</tr>
<tr>
<td>Vaessen et al. 2013</td>
<td>fMRI—functional network analysis</td>
<td>8-13</td>
<td>28 patients, 37 controls</td>
<td>FLE</td>
<td>Abnormal clinical MRI, other neurological disorder</td>
<td>Computerised visual searching task</td>
<td>Increased modularity score associated with worse performance on cognitive task</td>
</tr>
<tr>
<td>Lin et al. 2012</td>
<td>Structural MRI</td>
<td>8-18</td>
<td>13 patients, 54 controls</td>
<td>BECTS</td>
<td>Abnormal clinical MRI, other neurological disorder</td>
<td>D-KEFS—sorting test only</td>
<td>Increased putamen volume associated with improved executive function in patients.</td>
</tr>
<tr>
<td>Kassiri et al. 2011</td>
<td>Structural MRI</td>
<td>Unknown</td>
<td>24 patients</td>
<td>TS</td>
<td>All had medically intractable seizures, being investigated for epilepsy surgery</td>
<td>WISC-III</td>
<td>Association between number of cortical tubers and lower IQ</td>
</tr>
<tr>
<td>Tosun et al. 2011</td>
<td>Structural MRI</td>
<td>6-18</td>
<td>65 patients, 58 controls</td>
<td>Complex partial seizures</td>
<td>Abnormal clinical MRI, other seizure types, other neurological or metabolic disorder</td>
<td>WISC-III</td>
<td>Abnormal patterns of cortical thinning seen in patients with CPS and below average IQ scores</td>
</tr>
<tr>
<td>Caplan et al. 2010</td>
<td>Structural MRI</td>
<td>6-16</td>
<td>69 patients, 34 controls</td>
<td>Childhood absence epilepsy or complex partial seizures</td>
<td>Abnormal clinical MRI, other types of seizures, previous epilepsy surgery, other neurological or medical illness, IQ &lt;70</td>
<td>Test of Language Development-2</td>
<td>Language impairment in children with epilepsy is associated with reduced volume of superior temporal gyrus grey matter</td>
</tr>
</tbody>
</table>

Table 2 (continued)
<table>
<thead>
<tr>
<th>Study</th>
<th>Imaging modality</th>
<th>Age (year)</th>
<th>Number</th>
<th>Epilepsy type</th>
<th>Significant exclusions</th>
<th>Neuropsychological measurements</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caplan et al. 2009</td>
<td>Structural MRI</td>
<td>7-11</td>
<td>26 patients, 37 controls</td>
<td>Childhood absence epilepsy</td>
<td>Abnormal clinical MRI, other seizure types, atypical EEG, other neurological problem</td>
<td>WISC-III</td>
<td>Grey matter volumes associated with IQ in controls but not in patients</td>
</tr>
<tr>
<td>Pulsipher et al. 2009</td>
<td>Structural MRI</td>
<td>8-18</td>
<td>20 children with JME, 12 children with BECTS, 51 controls</td>
<td>JME/BECTS</td>
<td>Abnormal clinical MRI, other neurological or developmental problems, within 12 months of diagnosis</td>
<td>D-KEFS</td>
<td>Children with JME have executive dysfunction associated with reductions in thalamic volume</td>
</tr>
<tr>
<td>Caplan et al. 2008</td>
<td>Structural MRI</td>
<td>5-16</td>
<td>42 patients, 41 controls</td>
<td>Complex partial seizures</td>
<td>Abnormal clinical MRI other than MTS, other neurological or metabolic disorder, other seizure types</td>
<td>WISC-III, The Story Game</td>
<td>Reduced orbito-frontal grey matter volume is associated with increased thought disorder scores</td>
</tr>
<tr>
<td>Byars et al. 2007</td>
<td>Structural MRI</td>
<td>6-14</td>
<td>249 children, No control group</td>
<td>First unprovoked seizure</td>
<td>Acute symptomatic seizure, chronic medical condition of functional disability</td>
<td>Kaufman Brief Intelligence Test</td>
<td>Children with a significant lesion on MRI score significantly lower on IQ, language and verbal memory scales</td>
</tr>
<tr>
<td>Hermann et al. 2006</td>
<td>Structural MRI</td>
<td>8-18</td>
<td>53 patients with new-onset idiopathic epilepsy, 50 first degree cousins</td>
<td>Diagnosis of epilepsy within last 12 months</td>
<td>No other neurological or developmental conditions, abnormal MRI</td>
<td>Weschler Abbreviated Scale of Intelligence, D-KEFS, CMS</td>
<td>Reduced parietal and occipital grey matter volume in patients with epilepsy and cognitive problems</td>
</tr>
<tr>
<td>Lawson et al. 2000</td>
<td>Structural MRI</td>
<td>0-18</td>
<td>231 patients, 44 controls</td>
<td>Epilepsy referred for MRI</td>
<td>Neurodegenerative disorder, previous neurosurgery</td>
<td>School/Neurologist report</td>
<td>Cognitive impairment is associated with reduced total brain volumes.</td>
</tr>
</tbody>
</table>

Abbreviations: DTI, diffusion tensor imaging; fMRI, functional magnetic resonance imaging; BECTS, benign epilepsy with centro-temporal spikes; FLE, frontal lobe epilepsy; JME, juvenile myoclonic epilepsy; CAE, childhood absence epilepsy; MTS, mesial temporal sclerosis; TS, tuberous sclerosis; WISC-III, Wechsler intelligence scales for children–III; D-KEFS, Delis-Kaplan executive function scale; CMS, childhood memory scale; FA, fractional anisotropy; IQ, intelligence quotient.
as to the cortical areas involved, with different studies reporting changes within frontal (44), temporal (48) and parieto-occipital (45) lobes. Poorer executive function was associated with changes within the basal ganglia and thalami (49,50) and with reductions in temporal white matter integrity (51). Evidence from DTI and fMRI suggests that decreased white matter integrity along fronto-occipital tracts (52) as well as within the corpus callosum (51) and disrupted brain networks (53-55) may also be associated with impaired performance on cognitive and language tasks. One implication is that cognitive impairment in children with epilepsy may not be associated with alterations within a single brain region but a product of changes in anatomically diverse brain areas and affecting both grey and white matter.

This parallels the literature on cognitive ability in the general population which has also been linked to both grey matter volume (56) as well as white matter integrity (57). It has been suggested that cognitive ability is a distributed property of the brain and that white matter network connectivity is a key component (58,59) with more “efficient” network architectures associated with improved cognitive ability.

**Behaviour**

Two studies were identified from the initial search that looked at behavioural problems and neuroimaging in children with epilepsy and were considered applicable to this review (Table 3). These two studies, from the same group in Japan, looked at children with frontal lobe epilepsy (FLE) and BECTS (61), with and without behavioural problems and cognitive co-morbidity. However the limited number of patients with epilepsy and behavioural problems in each study (two patients in each study) preclude any formal statistical analysis being presented. In these two small longitudinal studies reduced frontal and prefrontal lobe growth was shown to be reduced in children with frontal lobe epilepsy (FLE)/BECTS and behavioural and cognitive problems over a 2-year period after initial presentation compared to children with FLE/BECTS and no impairments.

One additional study was identified from other references. This study, using the child-behaviour checklist, of 90 children with new-onset epilepsy found that higher social competence was associated with increased cortical thickness in the left superior frontal and left postcentral regions, whereas disruptive behavioural problems were associated with decreased cortical thickness predominantly in bilateral frontal regions and internalising behavioural problems (somatic disturbances, affective disorder, anxiety) were associated with fewer significant changes (62). No healthy control group was included and raw behavioural scores were not reported, so it is not possible to ascertain if these children were displaying more problems than the general population, although it is known that children with new-onset epilepsy are reported to show more problems than unaffected siblings using this checklist (16).

The evidence for a structural link between epilepsy and behavioural problems remains weak and no controlled studies have been performed; the existing data suggests that disruption of frontal lobe development may be a factor.

**Mood disorders**

Only one study was identified in the search that was considered applicable to this review (Table 3). Despite the substantial literature on amygdala/basal ganglia abnormalities and depression in adults with temporal lobe epilepsy (TLE) (63), little systematic study appears to have been carried out in a paediatric age group. The single study that has been performed (64) looked at children with active CPS and found that larger amygdala volumes were associated with a higher risk of affective disorder, a similar finding to that reported in the adult TLE literature (63) but in contrast to studies of major depressive disorder (65). Although they were unable to control effectively for IQ this raises the possibility that affective disorder in epilepsy may be distinct to mood disorders found in children without seizures and have a different pathophysiological basis.

**Neurobehavioural impairments**

One additional article by Lin et al. (66) was identified that looked at neurobehavioural impairments as a group in children with CAE and CPS (Table 3). They found an association between decreasing left thalamic volume and higher social problem scores for both epilepsy groups and a further association with lower IQ and language scores for children with CPS.

**Discussion**

Overall, there are a limited number of studies looking at the neuroimaging associations of neurobehavioural impairment in children with epilepsy. Most studies focus on either one particular type of epilepsy or a single impairment or both.
<table>
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<tr>
<th>Study</th>
<th>Imaging modality</th>
<th>Age (year)</th>
<th>Number</th>
<th>Epilepsy type</th>
<th>Significant exclusions</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kanemura et al. 2012</td>
<td>Structural MRI</td>
<td>4-8</td>
<td>6 patients, 11 controls</td>
<td>FLE</td>
<td>N/A</td>
<td>Two patients with FLE+ behavioural problems showed reduced prefrontal growth while seizures were active</td>
</tr>
<tr>
<td>Kanemura et al. 2011</td>
<td>Structural MRI</td>
<td>4-9</td>
<td>7 patients, 11 controls</td>
<td>BECTS</td>
<td>N/A</td>
<td>Two patients with BECTS+ behavioural problems showed reduced prefrontal growth while seizures were active</td>
</tr>
<tr>
<td>Dabbs et al. 2013</td>
<td>Structural MRI</td>
<td>8-18</td>
<td>90 patients, no control group</td>
<td>New diagnosis epilepsy</td>
<td>Other neurological or developmental problem, abnormal clinical MRI</td>
<td>Disruptive behaviours associated with decreased cortical thickness in bilateral superior frontal, caudal middle frontal and inferior parietal regions</td>
</tr>
<tr>
<td>Daley et al. 2008</td>
<td>Structural MRI</td>
<td>6-16</td>
<td>28 patients, 28 controls</td>
<td>CPS and cryptogenic epilepsy</td>
<td>Abnormal clinical MRI</td>
<td>Larger left amygdala volumes in children with CPS and affective/anxiety disorder</td>
</tr>
<tr>
<td>Lin et al. 2013</td>
<td>Structural MRI</td>
<td>6-16</td>
<td>CAE 21 children, CPS 20 children, 27 controls</td>
<td>Childhood absence epilepsy and complex partial seizures</td>
<td>Other forms of epilepsy, other neurological condition, intellectual impairment, abnormal clinical MRI</td>
<td>Left thalamic volume was associated with social problems in CAE and CPS groups and IQ and language ability in CPS group</td>
</tr>
</tbody>
</table>

Abbreviations: MRI, magnetic resonance imaging; FLE, frontal lobe epilepsy; BECTS, benign epilepsy with centro-temporal spikes; CPS, complex partial seizures; CAE, childhood absence epilepsy; IQ, intelligence quotient.
There are almost no studies looking at younger children under the age of 5 years and data looking at children with multiple impairments or significant learning difficulties is likewise extremely limited. The majority of studies exclude children with other neurological problems, known developmental problems or abnormalities on routine neuroimaging. Part of the reason may be because this group of children often have multiple medical/developmental comorbidities and are likely to require general anaesthesia for neuroimaging investigations, complicating their assessment. Exclusion of these children is however problematic as it is known that a high proportion of children with epilepsy have seizures caused by a known neurological condition or structural brain abnormality and that the clustering effect of neurobehavioural impairments mean that comorbidity is likely to be common. As analysis techniques improve, structural or neurological abnormalities need not be a priori grounds for exclusion, although technical refinements may be required. Therefore despite the methodological difficulties associated with working with this group of children it will be important that attempts be made to include them in future studies.

Cognitive impairment and executive function are the best studied impairments. There is now evidence from a number of studies that structural brain changes are present at or near to epilepsy diagnosis and that these changes can be associated with deleterious effects on cognition. The diversity of imaging methods reported make synthesis difficult: there is a general trend to the implication of multiple, anatomically distinct brain areas, but little agreement on which areas are important. Increasing evidence from advanced imaging techniques raises the interesting suggestion that the primary problem may be one of abnormal white matter connectivity and network disruption, rather than grey matter loss.

The five studies on ADHD in children with epilepsy also report the involvement of multiple cortical areas, with changes also noted in some subcortical structures such as the thalamus and brainstem. Other impairments are less well studied, with the scarce evidence available coming either from single, small studies or uncontrolled observational cohorts.

In summary, the small number of studies and disparate methodology make synthesis of the structural brain changes in epilepsy associated impairments difficult. There is a strong sense that network dysfunction is important, and that therefore imaging techniques that can assess this directly, such as fMRI and DTI are more likely to provide useful information, but the extent to which findings can be generalised across different epileptic syndromes and aetiologies remains to be determined. Likewise it remains uncertain the extent to which impairments in children with epilepsy differ from similar impairments in children without seizures. In view of the large number of epilepsy syndromes known, it will be important to understand how neurobehavioural impairments arise across different forms of epilepsy, especially those associated with early onset, structural lesions or multiple impairments. Ideally studies should assess children as near to diagnosis as possible to avoid confounding from the effects of seizures and medication. As neurobehavioural impairments have been found across almost all epilepsy syndromes, it will be important to move from studying isolated syndromes to broader studies including a range of different types of epilepsy. Studies focusing on these groups at greatest risk of impairments and with more severe impairments, for example on children with early onset epilepsy or with specific aetiological classifications, will be crucial in this regard. By including children with more severe and multiple impairments, although the power to detect syndrome specific changes will be lost, paradoxically power to detect associated structural brain changes may improve as more severe changes will be expected. Since many analysis techniques are still developing, the collection of a broad range of MRI data that will be able to accommodate future advances and analysis will be important to allow further information to be gained from existing cohorts as our understanding of these conditions advances. Correlating this with high quality neurocognitive and clinical data remains the key to unlocking the underlying neurological basis of these conditions and improving their diagnosis and treatment.

Regardless of methodology, the increasing awareness of neurobehavioural impairments and introduction of advanced quantitative neuroimaging techniques to traditional epilepsy cohorts mean that, while this is currently still a relatively unexplored area, it is one that is likely to undergo rapid expansion.

Disclosure: The author declares no conflict of interest.

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