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Author

Oyegbile, Temitayo O

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Targeted Review

The role of task-based neural activation research in understanding cognitive deficits in pediatric epilepsy

Temitayo O. Oyegbile *

Georgetown University Medical Center, Washington, D.C., United States of America

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ABSTRACT

Children with epilepsy can experience significant cognitive dysfunction that can lead to academic underachievement. Traditionally believed to be primarily due to the effects of factors such as the chronicity of epilepsy, medication effects, or the location of the primary epileptogenic lesion;, recent evidence has indicated that disruption of cognition-specific distributed neural networks may play a significant role as well. Specifically, over the last decade, researchers have begun to characterize the mechanisms underlying disrupted cognitive substrates by evaluating neural network abnormalities observed during specific cognitive tasks, using task-based functional magnetic resonance imaging (fMRI). This targeted review assesses the current literature investigating the relationship between neural network abnormalities and cognitive deficits in pediatric epilepsy. The findings indicate that there are indeed neural network abnormalities associated with deficits in executive function, language, processing speed, and memory. Overall, cognitive dysfunction in pediatric epilepsy is associated with a decrease in neural network activation/deactivation as well as increased recruitment of brain regions not typically related to the specific cognitive task under investigation. The research to date has focused primarily on children with focal epilepsy syndromes with small sample sizes and differing research protocols. More extensive research in children with a wider representation of epilepsy syndromes (including generalized epilepsy syndromes) is necessary to fully understand these relationships and begin to identify underlying cognitive phenotypes that may account for the variability observed across children with epilepsy. Furthermore, more uniformity in fMRI protocols and neuropsychological tasks would be ideal to advance this literature.

Key questions

1. How has task-based fMRI been primarily utilized in pediatric epilepsy?
2. What are the proposed mechanisms behind cognitive deficits in pediatric epilepsy?
3. What are the known relationships between task-based neural activation and cognitive deficits in pediatric epilepsy?
4. Could fMRI be useful/predictive in our clinical understanding of cognitive deficits in pediatric epilepsy?
5. What future research is required to improve our understanding of the relationship between fMRI and cognition in pediatric epilepsy?

1. Introduction

Over the last several decades, a rich literature has developed characterizing the nature and extent of cognitive comorbidities in adults with epilepsy [1–4]. There is now unequivocal evidence that these deficits extend to children with epilepsy as well [5–8]. Furthermore, similar cognitive deficits have been reported in healthy first-degree relatives, mainly siblings of patients with epilepsy, suggesting that the underlying neurobiological mechanisms leading to cognitive impairment may have a shared environmental or heritable component [13–17,86,110–112]. These deficits in patients with epilepsy can become manifest as impairments in day-to-day functioning and can negatively impact important life areas including academic achievement, job placement, and social interactions/relationships [18–22,45–47,113–115].

Cognitive impairment in pediatric epilepsy tends to persist and may progress across the entire course of the illness, often into adulthood, and is likely due to multiple factors [12,13]. This cognitive morbidity was traditionally believed to be primarily a manifestation of the long-term chronic effects of a multitude of factors that includes but not limited to multiple seizures, medication effects, degree of encephalogram

* Pediatric Neurology, Sleep Medicine & Epilepsy, Georgetown University, 4200 Wisconsin Ave NW, Washington DC 20016, United States of America.
E-mail address: sleep@healthpeak.net.

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(EEG) abnormalities, and focal effects of underlying lesions. However, recent evidence has suggested that there may be a preexisting abnormal neurobiological substrate that also serves as a significant contributor and might help to understand the evidence of cognitive and academic deficits prior to development of seizures (and, therefore, prior to any medication effects and seizure duration/frequency effects) [9–11], and the evidence of similar cognitive impairments in first-degree relatives. This underlying cognitive substrate has become the focus of more recent research, especially in new-onset mediation-naïve pediatric patients with epilepsy.

As a consequence, there has been a particular drive to better understand the development, specificity, and underlying mechanisms behind these deficits. Among the many tools that have been employed in this effort, task-based functional magnetic resonance imaging (fMRI) has emerged as a powerful resource to obtain information about specific changes in neural activity during a task. This change in neural activity is thought to reflect the underlying neurobiological processes required to perform a specific task and provides significantly better predictive data that are more robust and reliable than general brain network connectivity data [23,24]. Researchers have begun to use this neuroimaging tool to link identified alterations in neural signals with cognitive domain dysfunction including but not limited to anomalies in memory, language, and executive function, allowing for more in-depth characterization of cognitive comorbidities in clinical populations such as epilepsy.

This targeted review synthesizes current knowledge regarding the relationship between task-based fMRI abnormalities in pediatric epilepsy and associated anomalies in cognitive function in an effort to identify potential neural correlates of impaired cognition in children with epilepsy. This review uniquely focuses on the effort to further understand the effects of epilepsy on the developing brain and to begin to identify correlates of neural activity that are associated with cognitive comorbidities in youth with epilepsy.

Specifically reviewed here are studies utilizing task-based fMRI to better understand neurobiological correlates of cognitive deficits in epilepsy. Search terms included “fMRI”, “functional activation”, “task-based”, “neural activation”, “cognition”, “cognitive dysfunction”, “cognitive deficits”, “child”, “pediatrics”, “children”, “humans”, “epilepsy”, “seizure”, “neuropsychology”, “neuropsychological”, “memory”, and “attention”. Criteria for inclusion were (1) the use of task-based fMRI to measure neural activation, (2) inclusion of at least one group of pediatric patients with epilepsy and a comparison with healthy controls, (3) measurement of performance on at least one cognitive task, and (4) reported findings (either significant or null) of the relationship between task-based fMRI and cognitive performance within the pediatric epilepsy group. This review begins with a brief overview of the role that task-based fMRI has played in pediatric epilepsy and its limitations thus far. Next, briefly discussed are previous findings of cognitive abnormalities in pediatric epilepsy and the proposed underlying mechanisms, followed by a review of the studies reporting task-based fMRI abnormalities and cognitive deficits in pediatric epilepsy using the above criteria. Following that review, we then provide an examination of how these findings fit within the framework of current theoretical mechanisms of cognitive dysfunction in other brain disorders. The review concludes with a discussion of the limitations of current knowledge and then future directions including alternative approaches to research designs that may improve our knowledge and enable direct comparisons and future potential meta-analyses. To our knowledge, this is the first review of assessment of the relationship between task-based neural activation and cognitive dysfunction in pediatric epilepsy.

2. How has task-based fMRI been primarily utilized in pediatric epilepsy?

The role of functional neuroimaging in the clinical setting has become more precise and defined. In the field of pediatric epilepsy, task-based fMRI has primarily improved our ability to make decisions on epilepsy surgery [25–27] and has begun to shed light on the process of atypical language development in pediatric epilepsy [28–33,54] (see Table 1). The focus of fMRI in epilepsy has been primarily aimed at how functional neuroimaging can be used as a tool to explore surgical options in pediatric epilepsy, specifically to define a potential excisional epileptic focus and for language and memory localization prior to epilepsy surgery [34,35]. Language lateralization using task-based fMRI is regularly performed in children prior to surgery [99,100]. In addition, language-task fMRI identifies the language-dominant hemisphere and helps to interpret ambiguous cognitive (Wada Test) findings to determine the side of the lesions and seizures [26,36]. This is imperative to avoid significant cognitive deficits after surgery. As such, there are many studies focused on language lateralization, memory lateralization, and postsurgical outcomes using task-based fMRI [37,38,60]. We are beginning to understand the abnormalities in language lateralization associated with functional activation of specific networks while subjects perform specific tasks [60]. The evidence indicates that the age at onset of epilepsy or age at possible injury may play a role in language lateralization and verbal memory performance [39,40,60]. Furthermore, younger age at onset of seizures is associated with a higher likelihood of atypical language [39,40]. However, it is also well understood that cognitive impairment may still remain, develop, or even progress even after surgery [37].

While this information is very important and informative for surgery, it has led to a ‘pigeon-holing’ role for fMRI when, in actuality, it may provide much deeper and richer information in our understanding of the development of cognitive dysfunction in pediatric epilepsy in the clinical setting. Currently, potential surgical candidates are the only patients considered for fMRI in many if not most epilepsy clinics, and expanding that option to all patients with epilepsy may be very beneficial as the literature is beginning to suggest that functional neuroimaging may shed some light on potential mechanisms behind these cognitive symptoms.

3. What are the proposed mechanisms behind cognitive deficits in pediatric epilepsy?

Children with epilepsy are at increased risk of cognitive limitations and academic difficulties (see Table 2). Up to 26% of children with epilepsy have below normal cognitive function [6,41,53,82]. These children are also more likely to receive special education services compared with controls even after controlling for neurocognitive test scores [42,48,82] and display higher rates of academic problems compared with typically developing youth [48,87]. Even though the estimated rates vary considerably due in part to what is under investigation (e.g., intelligence, specific cognitive domains) and how the abnormality is defined (−1, −1.5, or −2 standard deviations below; or for intelligence quotient (IQ) studies scores under 80 or under 70, etc.), it is clear that cognitive deficits do indeed exist in the pediatric population with epilepsy.

This cognitive dysfunction is noted within multiple different pediatric epilepsy syndromes (see Table 2). Both generalized and focal epilepsies appear to be impacted [50,53,66,87,114]. Children with idiopathic generalized epilepsy [49,63] and childhood absence epilepsy exhibit evidence of cognitive impairment [61,63,65], even in drug-naïve patients [62,64]. Children with focal epilepsy including benign epilepsy with centrotemporal spikes (BECTS), frontal lobe epilepsy (FLE), and temporal lobe epilepsy (TLE) also show evidence of cognitive dysfunction [51,

Table 1
Current task-based fMRI utilization.

Current task-based fMRI utilization in pediatric epilepsy:
~ Lesion localization
~ Presurgical evaluation
~ Language and memory lateralization
~ Less invasive alternative to Wada Test testing

Table 2
The global nature of cognitive abnormalities in children with epilepsy based on review and population-based papers. 'x' indicates the tests that were performed in the study, which were abnormal. IGE = Idiopathic generalized epilepsy. LGS = Lennox gastaut syndrome.

Review/population-based paper	Study info	Findings by cognitive domain						
		Executive function	Language	Processing speed	Memory	Attention-deficits	IQ	Math
Lah et al., 2017 [5]	TLE, FLE, BECTS, IGE, absence		x		x		x	x
Nickels et al., 2016 [6]	West, LGS, FLE, TLE, IGE	x		x	x	x	x	
Braakman et al., 2011 [7]	FLE	x	x	x	x	x	x	
Jambaque et al., 2013 [50]	Multiple epilepsy types	x	x		x	x	x	
Davies et al., 2003 [43]	Behavior assessed in multiple epilepsy types					x		
Reilly et al., 2014 [44]	Behavior assessed in multiple epilepsy types					x		
Verrotti et al., 2015 [61]	Absence, IGE, BECTS	x	x		x	x	x	
Rzezak et al., 2014 [82]	TLE	x			x			
Verche et al., 2018 [53]	FLE, adults and children	x		x	x		x	

52,57,63,70–72,81,87]. The often-noted generalized nature of evident cognitive impairment in focal epilepsy suggests that the disorder involves more than just the specific lobe or focal lesion and that there may be an underlying processing abnormality affecting wider brain regions. The classic model suggested a tight linkage between lateralization/localization of the "lesion" and disruption of the cognitive skill supported by that region with relative sparing of other cognitive abilities. Over time, the literature has indicated that this clearly may not be the case [69,87]. Even the classic epilepsy models of generalized epilepsies such as an abnormality focused in executive function in absence or juvenile myoclonic epilepsy (JME) [61–65] have been questioned by careful meta-analyses [4].

Furthermore, in both children with new-onset epilepsy who are drug-naïve and those with chronic long-term poorly controlled epilepsy on multidrug regimens, cognitive deficits of differing degrees can be observed in multiple domains including IQ, episodic memory, working memory, executive functioning, language, processing speed, attention, and perception, suggesting a global nature to the cognitive deficits in spite of seizure history/course and effects of sedating medications [65,68,69].

The greater than expected widespread nature of the deficits across a wide variety of cognitive domains makes it difficult to establish a clear pattern of specific deficits associated with the disorder. In fact, the distributed nature of observed cognitive anomalies challenged the viewpoint that specific patterns of deficits are associated with the specific neurobiological correlates of the different epileptic syndromes. Instead, children with epilepsy, on average, consistently display anomalies ranging from 0.5 to 2.5 standard deviations below the mean of healthy children on neuropsychological tasks that measure a multitude of cognitive domains.

The underlying mechanisms behind these greater than expected cognitive findings in children with epilepsy are yet to be clarified, however, it is clear that multiple factors contribute to these findings (please see Table 3). It is clear that seizure duration and seizure frequency often play a role in the development and especially the progression of cognitive impairment. Multiple cross-sectional studies have shown that cognitive impairment may worsen with longer duration of epilepsy [55,57,127] including evidence of worsening memory, attention, and working memory associated with epilepsy duration [127]. Furthermore, seizures that are poorly controlled and difficult to treat even on multiple medication regimens can considerably contribute to cognitive dysfunction [128]. Multiple antiepilepsy medications including valproic acid, topiramate, levetiracetam, and barbiturates can also adversely affect cognitive performance [129]. Overall, this can lead to cognitive impairment in pediatric patients with epilepsy that can worsen over time with increasing duration of disorder, regardless of the initial cognitive/neuroimaging status [8,9,55–59].

Table 3
Current mechanisms behind cognitive deficits in pediatric epilepsy.

Current proposed mechanisms underlying cognitive deficits in pediatric epilepsy:
~ Seizure duration (chronic epilepsy)
~ Seizure frequency (poorly controlled epilepsy)
~ Antiepileptic medications
~ Focal lesions
~ Genetic/hereditary
~ Abnormal neural network development

More recent evidence has begun to emerge indicating that children with epilepsy exhibit academic abnormalities at the time or even before the time of diagnosis [48], and this cognitive impairment persists even when there is successful treatment of seizures and minimal cognition-altering antiepilepsy medication. This suggests that even when seizures and medication are minimized, cognitive impairment may still exist and persist. These maturing epileptic brains may not benefit from normal developmental processes involving plasticity, reorganization, and protection of their cognitive function compared with their typically developing counterparts [8,9]; however, the relationships between this abnormal neural development and the ensuing cognitive dysfunction are poorly understood currently. These more recent findings suggest that this generalized cognitive dysfunction may be the result of, or associated with, a disruption in the connectivity of specific intrinsic networks due to abnormalities within specific brain regions. Measuring the relationship between the impairments in specific cognitive domains with abnormalities in neural activation during task-based fMRI may reveal patterns of brain–behavior relationships in patients with epilepsy that may support the notion of a neural substrate mechanism underlying the development of cognitive deficits in this population.

4. What are the known relationships between task-based neural activation and cognition in pediatric epilepsy?

Imaging in pediatric epilepsy has shown a wide range of findings. Often, these children have normal clinical imaging while others show lesional abnormalities. Regardless of clinical imaging status, when quantitative analysis is performed, structural brain abnormalities are frequently noted in children with epilepsy compared with their typically developing peers. Cognitive deficits in pediatric epilepsy have been reported to be associated with these structural brain abnormalities such as decreased overall brain volumes, decreased gray matter and white matter, and abnormal cerebrospinal fluid [77–79], similar to the adult literature [12,103]. Potentially, these volumetric and quantitative abnormalities may be a result of, or associated with, decreased connectivity of intrinsic networks between specific brain regions causing decreased neural activation during specific tasks;, ultimately resulting in cognitive dysfunction in multiple cognitive domains. This dysregulated network activity and connectivity may result in reduced neuron activation and eventually volume loss [116]. More extensive research is needed to substantiate this potential mechanistic model. Specifically, examination of the neural activity associated with these intrinsic brain networks through functional neuroimaging tools provides a unique opportunity to understand and characterize abnormalities in brain networks that would not ordinarily be clearly distinguished through

examination of cognitive performance on neuropsychological testing [80]. As a result, the application of functional activation methods to assess intrinsic brain networks is paramount to elucidate cognitive deficits in pediatric epilepsy [81]. Here, we present the relationship between fMRI and cognition via specific cognitive domains. Within each domain, we present the cognitive findings, the task-based fMRI activation findings, and the associated relationships (also see Table 4).

4.1. Executive function (working memory/attention)

4.1.1. Neuropsychological testing

Children with both focal and generalized epilepsy exhibit significant executive dysfunction [62,67,73–75,82]. Our group showed poorer performance on the Delis–Kaplan Executive Function (D-KEFS) color word and card sort testing in patients with TLE compared with healthy controls [83]. On behavioral testing, Bechtel et al. showed poorer performance in children with epilepsy during working memory tasks with higher cognitive load compared with tasks with lower cognitive load [76]. There has, however, been some inconsistency in the findings of working memory deficits in children with epilepsy. Pascalicchio et al. show deficits in digit span (working memory) in children with juvenile myoclonic epilepsy [84] while others have found no deficits [85]. These inconsistencies may potentially be clarified by cognitive phenotyping, which exposes differential cognitive abilities in different individuals with the same epilepsy type.

4.1.2. Task-based fMRI activation

Our team evaluated the executive control network (ECN, see Fig. 1) and the default mode network (DMN, see Fig. 2) to assess for multiple brain network disruptions during a working memory (*N*-back) task [83,88]. In functional imaging research, working memory is frequently investigated using the '*N*-back' task, which involves monitoring a series of letters or pictures and responding whenever the stimulus is presented *N* trials prior [125]. The '*N*' instruction regularly changes throughout the task requiring constant online monitoring and updating of information. This *N*-back paradigm is processed through the ECN that includes both bilateral frontal and parietal cortical regions (see Fig. 1) [126]. Brain regions involved in the DMN include the medial prefrontal cortex, posterior cingulate cortex, lateral and medial temporal lobes, and posterior inferior parietal lobule (see Fig. 2) [123,124].

The ECN is a task positive network that activates during a working memory task while the DMN is a network that deactivates during such a task. Our results show that children with TLE exhibit less activation in the left frontal lobe in the ECN compared with healthy controls. In addition, there was significantly less deactivation of the DMN, primarily in the precuneus/posterior cingulate cortex compared with controls while performing the same working memory task. Bechtel et al. also assessed executive function in epilepsy using task-based fMRI activation [76]. They demonstrated that boys with epilepsy and attentional concerns recruited substantially less cortical regions required for working memory performance (frontal and parietal lobes) compared with healthy controls, including the insular region and cingulate.

4.1.3. Relationship between neural activation and working memory

Our group specifically assessed the direct correlations between neuropsychological testing and neuroimaging data using regression analysis [83,88]. Decreased activation of the ECN (left superior parietal lobe, left inferior frontal gyrus, right superior frontal gyrus) in children with

Table 4
Summary of studies reporting a relationship between neural activation and cognitive function. *D-KEFS = Delis–Kaplan Executive Function System, CELF-IV = Clinical Evaluation of Language Fundamentals 4th edition, CTPP = Comprehensive Test of Phonological Processing, WRAT-III = Wide Range Achievement Test 3rd edition, WMS = Wechsler Memory Scale, CMS = Children's Memory Scale, WISC-IV = Wechsler Intelligence Scale 4th edition, WIAT = Wechsler Individual Achievement Test, EOWPVT = Expressive One Word Picture Vocabulary Test, CVLT-C = California Verbal Learning Test for Children, TEA-Ch = Everyday Attention for Children test, ROI = Region of Interest.

Study	Epilepsy syndrome	Sample size	Cognitive tasks	fMRI task	Networks	Analysis	Findings (in patients with epilepsy)
Cognitive domain: executive function							
Oyegbile et al. 2018	TLE	Epi = 15, Controls = 15	D-KEFS	*N*-Back	Executive control network (ECN)	Whole brain analysis	Decreased activation of the ECN is associated with poorer performance
Oyegbile et al., 2019	TLE	Epi = 15, Controls = 15	D-KEFS	*N*-Back	Default mode network (DMN)	Whole brain analysis	Reduced deactivation of the DMN is associated with poorer performance
Cognitive domain: language							
Vannest et al., 2012	BECTS	Epi = 15, Controls = 15	CTPP CELF	Semantic decision & Prosody discrimination	Language network/lateralization	ROI-based & Lateralization index	Nonlanguage regions are associated with better performance
Malfait et al., 2015	BECTS	Epi = 15, Controls = 18	WISC-IV WIAT EOWPVT CVLT-C TEA-Ch D-KEFS	Sentence reading comprehension	Reading network	ROI-based	Typical language activation predicts accuracy
Lillywhite et al., 2009	BECTS	Epi = 20, Controls = 20	CELF-IV WRAT-III	Verb generation	Language network/lateralization	ROI-based & Lateralization index	Left language lateralization is associated with better language test performance
Cognitive domain: processing speed							
Oyegbile et al., 2018	TLE	Epi = 15, Controls = 15	D-KEFS	*N*-Back	Executive control network (ECN)	Whole brain analysis	Decreased activation of the ECN is associated with longer reaction times
Oyegbile et al., 2019	TLE	Epi = 15, Controls = 15	D-KEFS	*N*-Back	Default mode network (DMN)	Whole brain analysis	Reduced deactivation of the DMN is associated with longer reaction times
Cognitive domain: memory							
Everts et al., 2010	TLE FLE	Epi = 40, Controls = 18	WMS CMS	Verbal fluency task	Language lateralization	ROI-based	Atypical language lateralization is associated with poorer verbal memory performance

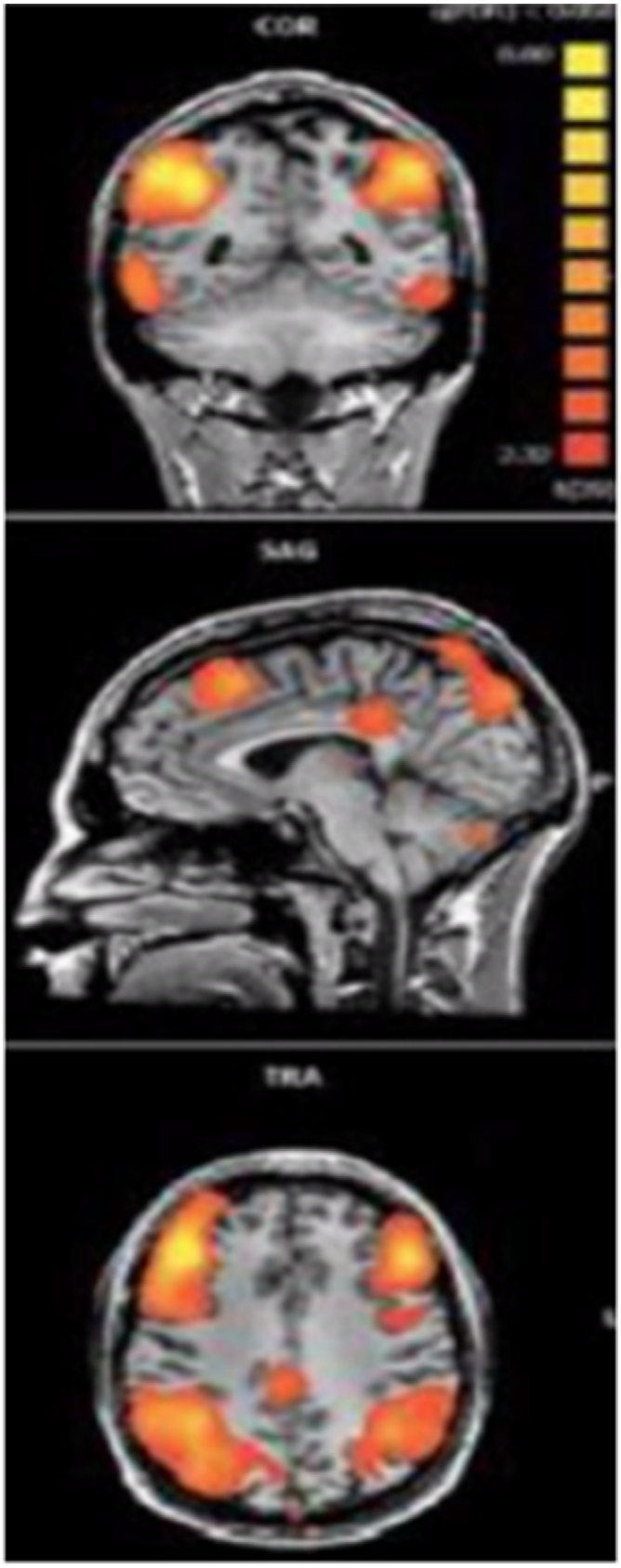

Fig. 1. Typical Executive Control Network noted in typically developing individuals [106].

TLE was associated with decreased accuracy and reduced speed on D-KEFS color word interference. There were also significant positive correlations of behavioral performance (accuracy and speed) and neural activation (in the left inferior parietal lobe, left inferior frontal gyrus, and right superior frontal gyrus) during the task such that higher accuracy and higher speed were associated with higher activation on the task. Our group also demonstrated that in children with TLE, decreased deactivation of the DMN is also significantly correlated with reduced accuracy and speed on the D-KEFS color word interference as well as the

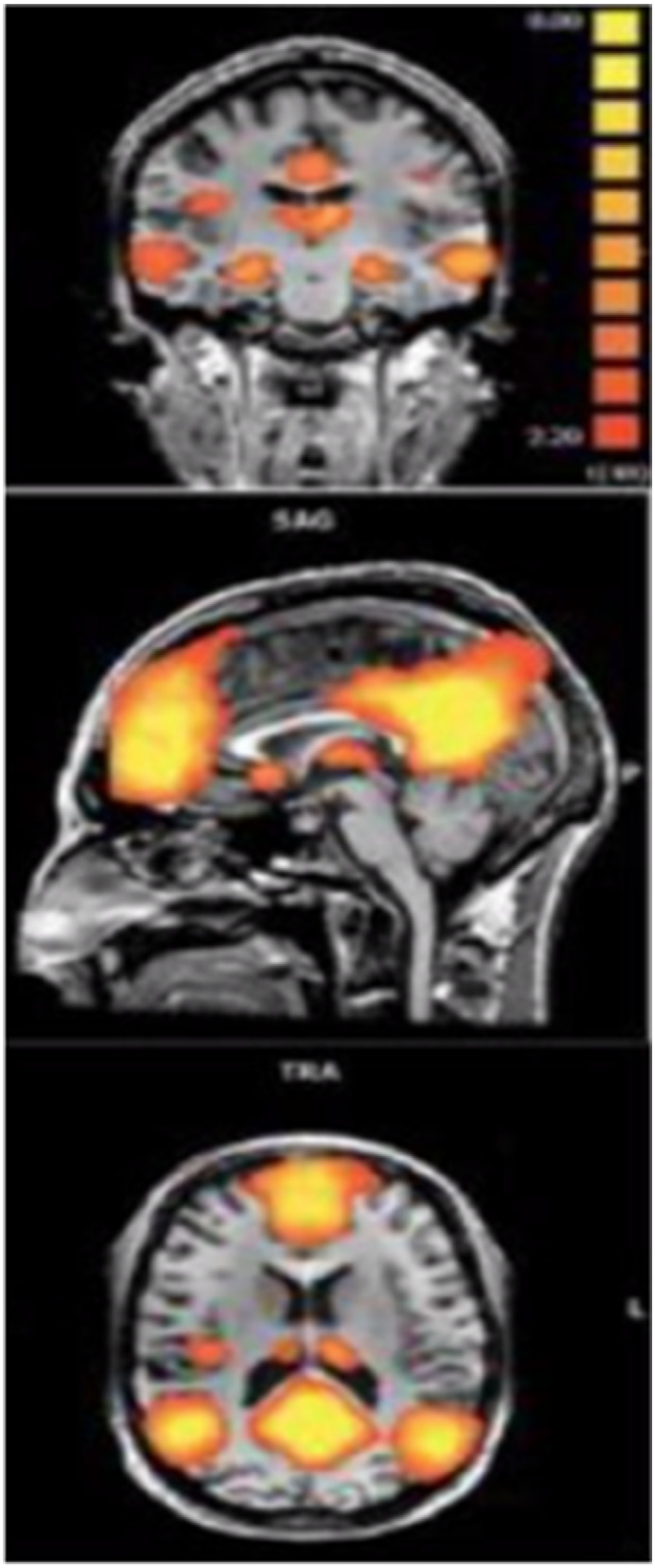

Fig. 2. Typical Default Mode Network noted in typically developing individuals [106].

D-KEFS card sort test. There were also significant negative correlations between behavioral performance (accuracy and speed) and neural activation during the task, such that less deactivation of the DMN was associated with less accuracy and longer reaction times in the performance of the working memory task.

4.2. Language

4.2.1. Neuropsychological testing

The relationship between language impairment and fMRI activation research in the pediatric epilepsy literature have focused primarily on children with BECTS and TLE. Benign epilepsy with centrotemporal spikes is an epilepsy syndrome that does not have a clear surgical option and frequently resolves over time while TLE has an opposite trajectory as it frequently does have a clear surgical option and frequently does not resolve over time. Children with BECTS exhibit lower language skills compared with healthy controls [89–91]. The language impairments are both receptive [92,93] and expressive [94,95], and both oral and written [96,97]. Siblings without epilepsy can also appear to also have similar pattern of cognitive impairment [98]. As discussed earlier, children with epilepsy frequently exhibit significant atypical (right-sided or bilateral) language lateralization [33,40,60].

4.2.2. Task-based fMRI activation

Children with BECTS show less consistent activation of the left hemisphere compared with healthy controls during multiple language tasks [89,90,102]. Vannest et al. showed that children with BECTS show more activation in the right hemisphere with decreases in the left hemisphere regions that typically are engaged in language tasks [89]. This suggests an atypical bilateral network for semantic processing as these patients may need to employ their right hemisphere language areas to successfully perform the task. Malfait et al. also showed higher activation in various regions not traditionally associated with language function suggesting that these patients with epilepsy recruited a broader network to perform the task including regions such as the bilateral precuneus, left supplementary motor area, and left caudate and putamen [90]. Oser et al. also showed an atypical bilateral language activation pattern in children with BECTS during a language task compared with controls who demonstrate typical left lateralization activation during language tasks [102] (see Fig. 3). These studies all suggest functional reorganization of the neural architecture for language function in children with BECTS. Other pediatric epilepsy syndromes, including focal and generalized epilepsies, show comparable findings as well [60]. Mankinen et al. found similar altered neural activation during language tasks in children with TLE compared with healthy controls [101]. Increased right hemispheric activity was noted in children with TLE during language tasks compared with controls, specifically within the right temporal structures, thalamus, and basal ganglia. Children with epilepsy also show significant alterations in the DMN, which is a typically deactivated network during language tasks. Specifically, children with BECTS show decreased deactivation of the DMN (precuneus region) during language tasks. Overall, this indicates disruption of multiple brain networks.

4.2.3. Relationship between neural activation and language

The relationship between language tasks and fMRI activation provides insight into neural processing in children with epilepsy. During one language task (semantic decision task, where participants hear single words and make a button-press response if the item has target semantic properties, alternating with a control tone decision task where participants responded with a button-press to a target sequence of tones [89]), the left anterior prefrontal cortex and the precuneus/posterior cingulate cortex had a positive correlation to performance in healthy controls while the right inferior frontal gyrus had a negative correlation [89]. On the other hand, children with BECTS showed an increase in activation of the left parahippocampal gyrus and lingual gyrus bilaterally that correlated with better cognitive performance while

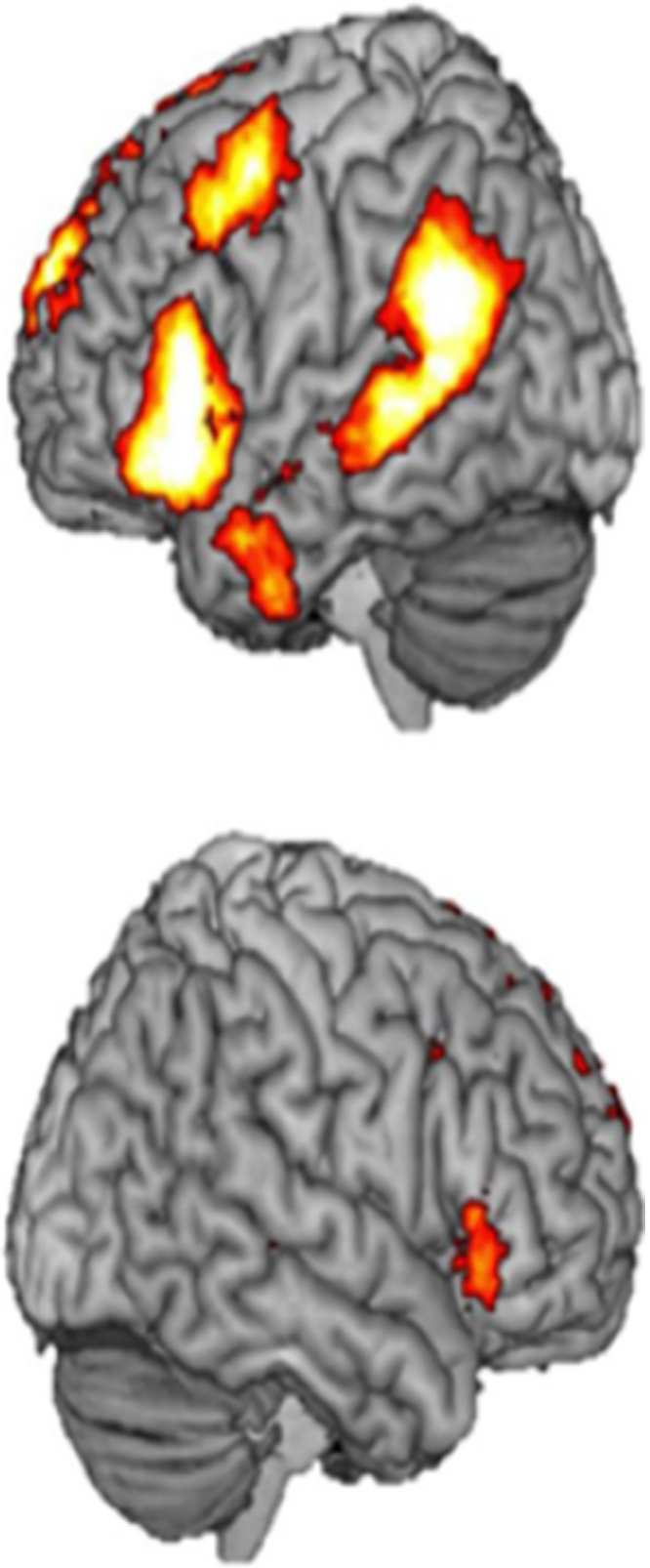

Fig. 3. Typical Language Network noted in typically developing individuals. Note the principal activation regions are within the left hemisphere, compared to the right hemisphere [105].

there was a negative correlation with activation in the left supramarginal gyrus. It appears that the striatum and visual regions were associated with better performance in children with BECTS while better performance was associated with increase in the cingulate cortex

activity and decrease in the right frontal lobe activity in controls. This suggests different strategies to perform the task. The task performance was better in controls suggesting that the controls employ a more efficient network process. Controls rely on regions associated with attention and response monitoring and not on regions supporting processing linguistic stimuli. On the other hand, children with epilepsy may be drawing on additional strategies such as relying on visual imagery by engaging the visual cortex.

In another language task (prosody discrimination task, where participants were presented with audiovisual sentence stimuli and indicated with a button press whether the sentence is a statement or question [89]), controls and children with epilepsy with increased activation in the medial frontal and anterior cingulate cortex had better performance, however, only children with epilepsy showed an increase in activation of the parietal regions bilaterally (atypical), also associated with better performance [89].

Even though patients with epilepsy and healthy controls performed similarly on the tasks in the Malfait et al. study, they showed that predictors of accuracy in healthy controls included activation of typical language regions (left frontal lobe) which was not observed in the patients with epilepsy [90]. They also showed that patients with epilepsy exhibit a more heterogeneous contribution of brain networks to task performance compared with healthy controls. Furthermore, Lillywhite et al. demonstrated that among children with BECTS, better performance on a sentence production test and higher reading scores were correlated with increasing left sided lateralization [12,104].

4.3. Processing speed

4.3.1. Neuropsychological testing

Children with epilepsy frequently demonstrate slowed responses on fMRI tasks [83,88,89,107]. On detailed testing, our group showed poor performance on speedy dexterity in children with TLE compared with healthy controls [83].

4.3.2. Task-based fMRI activation

To our knowledge, no study has assessed neural activation directly associated with speeded tasks in children with epilepsy.

4.3.3. Relationship between neural activation and processing speed

Decreased activation of the ECN, specifically in the left superior parietal lobe, left inferior frontal gyrus, and right superior frontal gyrus in children with TLE was associated with reduced speed and dexterity on pegboard testing [83]. Deactivation of the DMN is also associated with processing speed. A negative correlation showed that children with longer reaction times during a working memory task exhibited less deactivation of the DMN, specifically within the left posterior parietal lobe, posterior cingulate cortex, right medial prefrontal cortex, and left parietal lobe [88].

4.4. Memory

4.4.1. Neuropsychological testing

Children with epilepsy frequently show memory deficits. Children with focal epilepsy show below average verbal memory performance (word pairs learning and word pairs recall) compared with healthy controls [108,109]. However, Mankinen et al. found no cognitive differences in memory-related tasks in children with TLE, compared with controls [101], which may be due to differences in cognitive phenotypes that describe differential cognitive abilities in different individuals with the same epilepsy type.

4.4.2. Task-based fMRI activation

To our knowledge, no study has assessed neural activation directly associated with memory in children with epilepsy.

4.4.3. Relationship between task-based fMRI activation and memory

As mentioned earlier, atypical language dominance (bilateral and right-sided) is more likely in children with epilepsy compared with healthy controls. There is a strong correlation between verbal memory performance and language lateralization in children with left-sided epilepsy [108]. Atypical language lateralization was associated with improved verbal memory performance. In addition, verbal memory performance may predict language lateralization.

5. Could fMRI be useful/predictive in our clinical understanding of cognitive deficits in pediatric epilepsy?

This is the first review assessing the relationship between task-based neural activation and cognitive/neurobehavioral deficits in pediatric epilepsy. The findings above certainly demonstrate that fMRI has the potential to be useful in expanding our clinical understanding of cognitive deficits in pediatric epilepsy. It also shows that fMRI can extend neuropsychological test findings by providing mechanistic patterns that may underlie this cognitive dysfunction in childhood epilepsy. Further investigation is required to fully characterize all these potential relationships. Even though clear conclusions cannot be made with this limited information, it does suggest that fMRI may prove useful clinically to improve our understanding of cognitive deficits in different pediatric epilepsy syndromes.

Other brain-related disorders have also shown benefits of more extensive assessment of cognition via functional neuroimaging. In Alzheimer's research, longitudinal cognitive scores within individuals (specifically Mini Mental State Examination scores) have been associated with functional brain network changes and have even been related to factors such as cerebrospinal fluid biomarkers [119,120]. Furthermore, schizophrenia studies have performed direct correlations of individual cognitive domains and functional activation that has provided insight into potential predictors of relapse or deterioration/progression [117,118]. The adult epilepsy literature has begun to elucidate the connections between cognition and neural networks via functional neuroimaging more than the pediatric epilepsy literature [121,122]. Because it is becoming clearer that the cognitive deficits may precede the manifestation and presentation of the epilepsy [8,9,11], it would certainly be beneficial to determine the network abnormalities that precede or concurrently develop with the development of cognitive deficits and the manifestation of seizures. Based on this, further investigation within a pediatric epilepsy population would be ideal.

6. What future research is required to improve our understanding of the relationship between fMRI and cognition in pediatric epilepsy?

There is a dearth of knowledge and further information that can be gleaned from using task-based fMRI to understand cognitive impairment in epilepsy and the developing brain. At this point, the literature is so sparse that it is imperative to successfully replicate the findings that have been documented and extend the findings further (see Table 5). If researchers can replicate and extend these specific patterns, it is possible to better characterize the cognitive impairment and use this knowledge to develop better prediction models and treatment

Table 5
Summary of best approaches for future research.

Approaches to future research:
~ Shared protocols for task-based fMRI studies - e.g., motion correction in children
~ Uniformity of methods/cognitive tasks inside and outside the fMRI scanner
~ Comparison of neuropsychological tests to fMRI findings
~ Comparison of multiple epilepsy syndromes
~ Assessment of cognitive phenotypes and heritability of the cognitive dysfunction
~ Increase sample size and number of studies for adequate reliability and validity
~ Longitudinal studies

options, with a focus on treatment of cognitive impairment along with the treatment of seizures.

It is important to note that the studies discussed above all have small sample sizes and only evaluate children with focal epilepsies. In addition, unfavorable contributions from seizure frequency, duration, and antiepileptic medications are not always acknowledged or discussed. These clinical characteristics play a major role in cognitive assessment and could, therefore, play a large role in neural activation findings. Also, the limited available data employ different methods in both fMRI protocols and neuropsychological tests. A uniformity to the methods would be beneficial to compare findings across centers and studies. For instance, motion correction, which is often used to improve motion artifact in pediatric fMRI studies, is not consistently utilized in all the studies above. Clear protocols on how to handle motion correction in pediatric fMRI epilepsy studies would improve consistency and assist in integration/comparison of future studies. Another key methodological difference was the variety of tasks used to measure each cognitive domain. Some researchers relied only on fMRI paradigms to assess cognition (i.e., no formal neuropsychological testing outside the scanner) while others performed traditional neuropsychological tests outside of the scanner. Others yet chose to conduct neuropsychological testing but did not directly compare it to the fMRI findings. With more pediatric epilepsy literature demonstrating and validating the usefulness of relating standardized cognitive batteries to neural network activation, we will be able to better characterize the neurodevelopmental mechanisms underlying cognitive impairment in neurologic disorders, which will in turn inform future prevention and interventional treatment options. Measuring and comparing multiple cognitive domains and multiple neural networks (directly related and not directly related to the cognitive domain under evaluation) within the same study would also be of benefit to the field and would ease comparisons across studies. This would inform on the multinetwork dysfunction hypothesis that has been developed over the last few years.

Longitudinal studies that assess task-based functional activation, cognitive ability, and maturity across development would also be a powerful tool to assess the progression of abnormal brain development leading to cognitive deficits ending in real-world functional decline. Genetic/heritability studies assessing heritability of cognitive phenotypes and endophenotypes using first-degree relatives without epilepsy such as siblings, would also be beneficial to further our understanding of the relationship between cognition and neural networks. More recently, the concept of cognitive phenotypes has begun to shed light on potential new approaches to cognitive assessment in children with epilepsy. The concept of cognitive phenotyping suggests that the 'average' performance of patients with epilepsy may reveal an overall generalized impairment pattern, however, when individual performances are assessed in detail, it is clear that specific subpopulations of these patients with epilepsy show cognitive/behavioral problems of discrete types while other individuals do not. This variability across patients suggests that cognition can be phenotyped and its underlying neurobiology identified. If researchers can hone in on these specific patterns, we can characterize cognitive impairment better and use this knowledge to develop better prediction models and treatment options, with a focus on treatment of cognitive impairment along with the treatment of seizures [67,69]. Much larger sample sizes and longitudinal analysis in these studies would be necessary to successfully begin to explain the variability in cognition among children with the same syndrome.

Key questions (answered)

1. How has task-based fMRI been primarily utilized in pediatric epilepsy?

The known task-based fMRI findings are limited and primarily focus on surgical populations. Functional magnetic resonance imaging in clinical pediatric epilepsy is used primarily for presurgical evaluation and localization/lateralization of the epileptic focus/lesion.

2. What are the proposed mechanisms behind cognitive deficits in pediatric epilepsy?

The current literature shows that cognitive deficits are global and widespread in pediatric epilepsy regardless of whether the epilepsy is generalized or focused, chronic or newly diagnosed, drug-naïve or on polytherapy. These cognitive limitations are associated with academic underachievement in school settings. It is well-established that prolonged seizure duration, increased seizure frequency, antiepileptic medications, and focal lesions (neural substrate) contribute to the development and more importantly, the progression of cognitive impairment.
The most recent literature has begun to assess hereditary factors (as first-degree relatives also show cognitive impairment) and abnormal neural network development. Emerging literature suggests that abnormal neural network development may explain the presence of cognitive dysfunction in children, which antedates the manifestation of seizures and may also be responsible of the global wide-ranging pattern of cognitive impairment due to the intricate interconnectivity between and within the neural networks.

3. What are the known relationships between task-based neural activation and cognition in pediatric epilepsy?

The literature evaluating the relationship between neural activation and cognitive dysfunction has been very limited. Here, we present a total of six studies that assess the relationship between task-based neural activation within the fMRI scanner and neuropsychological testing outside of the scanner. The cognitive domains that have been assessed are executive function, language, processing speed, and memory. Overall, abnormal activation within both directly related and less related neural networks correlates with cognitive dysfunction. Overall findings and associated inferences are very limited at this point.

4. Could fMRI be useful/predictive in our clinical understanding of cognitive deficits in pediatric epilepsy?

Based on the limited available pediatric literature as well as the more extensive adult neurologic disorder literature, it is clear that fMRI can be very useful in improving our understanding of cognitive dysfunction in pediatric epilepsy.

5. What future research is required to improve our understanding of the relationship between fMRI and cognition in pediatric epilepsy?

Shared fMRI protocols, standardized neuropsychological tests, larger sample sizes, and direct comparisons between neural activation and neuropsychological tasks are necessary to move the field forward. Including potential adverse contributions of medications and chronicity of epilepsy in publications would also assist in comparing studies. In addition, further evaluation of cognitive phenotypes and endophenotypes using neural networks would be ideal to further understand the variability in cognitive abnormalities in pediatric epilepsy.

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