EPILEPSY OUT OF CONTROL

When frontal lobe epilepsy becomes more than seizures

Lydia van den Berg

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TABLE OF CONTENTS

CHAPTER 1

General Introduction

BACKGROUND

Epilepsy is an extensively investigated, and the most common neurological disorder presenting during childhood, with a prevalence of approximately 3 to 6 per 1000 in developed countries [1]. The International League Against Epilepsy (ILAE) defines epileptic seizures as ,"a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain,". It defines epilepsy as a neurological disorder characterized by an ,"enduring disposition of the brain to generate epileptic seizures," [2]. The ILAE recently updated the Classification of the Epilepsies [3,4]. This new classification is a multilevel classification, designed to cater to classifying epilepsy in different clinical environments (figure 1).

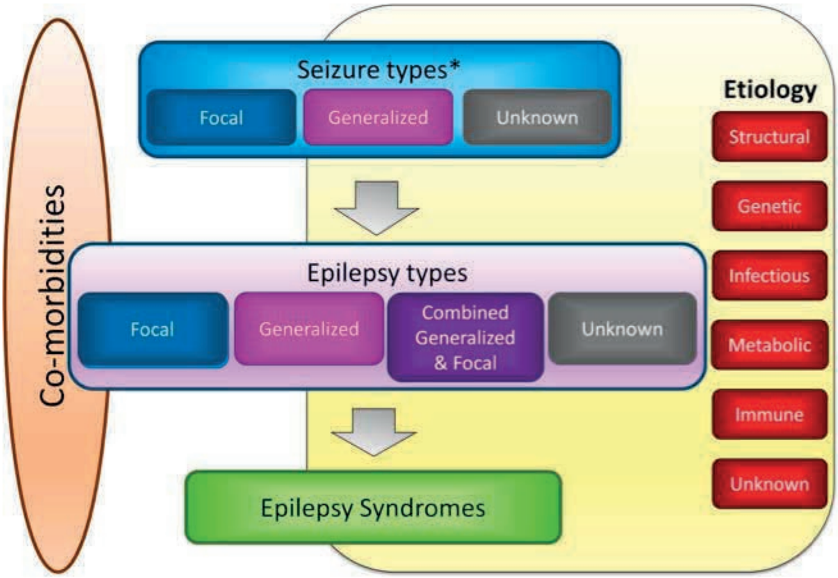

Figure 1: Framework for classification of the epilepsies. *Denotes onset of seizure [2].

Although the classification of seizures started a long time ago [4,5], the incidence and prevalence of the specific seizure types and epilepsy syndromes are still less well documented [1]. Nowadays, the ILAE classifies two different seizure types:

- focal seizures: are limited to specific areas of the brain. Further distinctions in the description of focal seizures relate to the lateralization (left vs right hemisphere onset) and to the topographical lateralization (frontal, temporal, occipital, parietal, central or a combination of these).
- generalized seizures: involve both hemispheres. Seizures may start as focal in one hemisphere, but spreads instantly to the other hemisphere.

It is thanks to Jackson in the late 19th century that we began to understand the anatomical implications of focal seizures [5]. Before, minor or ,"incomplete,"

seizure types were mostly treated as unimportant and dismissed as ,“epileptiform,“. Furthermore, Jackson made one realize that different brain structures are associated with specific types of seizures.
Manifestations of certain seizures are age-specific and depend on the maturation of the brain. Previous classifications have been based on anatomy, with temporal, frontal, parietal, occipital, diencephalic, or brainstem seizures. However, modern research changed our view of the pathophysiologic mechanisms involved and has shown epilepsy to be a network disease and not only a symptom of local brain abnormalities [6]. Furthermore cognitive and brain abnormalities of focal epilepsies do not always seem to respect pathophysiological boundaries [7]. A network paradigm is becoming increasingly useful for understanding the neural underpinnings of cognition [8]. Studies identified distinct functionally coupled systems and these systems include a central-executive network (CEN) anchored in dorsolateral prefrontal cortex (DLPFC) and the posterior cingulate cortex (PPC), and a salience network (SN) of default mode network (DMN) anchored in anterior insula (AI) and anterior cingulate cortex (ACC) [9,10]. Especially the frontal lobe is involved in these networks. The findings in these studies highlight early adolescence as a period of significant maturation for the brain’s functional architecture. Interruption of this development, by any means, might therefore be a major risk factor. The development of EF continues throughout this period lagging behind the development of other cognitive skills [22]. Therefore, this period may mark a period of particular vulnerability for developing executive dysfunction.

Cognition and behavior in pediatric epilepsy

Although epilepsy can have its onset at any age, children are over-represented in this group. A major area of concern is the cognitive development of these children. Epilepsy is suggested to interfere with the developmental trajectory of brain networks underlying cognition and behavior [12-15]. In terms of clinical outcome, emerging evidence shows a variety of cognitive dysfunction [15,16], behavioral and socioemotional changes and psychiatric comorbidity [17]. Moreover, the underlying brain pathology of epilepsy and its dynamics and even a bidirectional relationship between behavioral and cognitive disorders and epilepsy have been suggested [18,19].
Studies about cognitive functioning on (focal) epilepsy have focused highly on temporal epilepsy, revealing neuropsychological deficits for this specific focus [15]. As a consequence, conclusions about the cognitive profile and behavior might give a distorted and less valid view for other epilepsies. This might also account for advice and treatment. In clinical practice, especially children with frontal lobe epilepsy (FLE) seem vulnerable for developing behavioral disorders, which can be expected as disruption in the frontal lobe is in general related to behavioral changes [20]. It is not uncommon for these children to present (highly) disturbed behavior [21]. Moreover, although the intelligence profile in this

children remains within average range and memory and language functions are not deviant, learning problems are reported often [21,22].

In the present thesis the general aim is to investigate the association between FLE in school-aged children, neurocognitive problems and behavioral issues in order to give direction in developing interventions for patients and their caregivers. More specifically, the focus lies on particular aspects of executive functioning and adjoining behavior. In the following sections, the main concepts in this thesis will be explained in more detail. In the end of this introduction, the specific aims of the investigation will be summed up.

Frontal lobe (epilepsy)

To comprehend the complexity of FLE it is essential to understand more about de frontal lobes, more specifically, the prefrontal cortex (PFC). This can be subdivided globally into different subdivisions: dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLPC), orbitofrontal cortex (OFC), ventromedial prefrontal cortex (VmPFC) and dorsomedial prefrontal cortex (dmPFC). Growing evidence suggests that the prefrontal cortex is part of a broader functional system, which involves other brain regions and networks [22,23].

The frontal lobe helps regulating executive functioning processes with the rest of the brain, through the integrity of the connections of the frontal lobe with striatum [24], basal ganglia [25], nucleus caudatus [26], temporal lobe [27], hippocampus [28], and the cerebellum [29]. From a behavioral and cognitive perspective there are three frontal-subcortical circuits to consider [30], the DLPFC, the OFC and the anterior cingulate cortex (ACC). The DLPFC is mostly involved in planning, attention, working memory, the so- called executive functions; the OFC is involved in emotional processing and regulation of social behavior; the ACC participates in motivation, drive and initiative [30]. It is therefore not surprising that dysfunction of one or more of these circuits are related to different cognitive and behavior dysfunction [31]. Much of the research in this field was conducted in patients with traumatic brain injury (TBI), where specific parts of the brain are affected, although focal damage can have a more widespread effect if the damage affects regions, which are important for the communication between networks [32].

As mentioned above, the current view is of epilepsy being a network disease. Moreover, in many patients there is no specific area to be found in which the epilepsy is originated and whereby the epilepsy is widespread in a large area [33]. Especially FLE can be characterized by a rapid spread of seizure activity as a result of the extensive network of connections between the frontal lobe and other cortical and subcortical areas [34]. This may imply that with enduring seizures, more than one of the frontal-subcortical circuits is dysfunctioning and consequently leads to cognitive and behavioral disturbances. Indeed, different studies show decreased functional connectivity in FLE [15].

FLE accounts for 20 to 30 percent of all focal epilepsies [35] with an average

age at onset of FLE ranging from 4.6 to 7.5 years [22]. Typically of this type of epilepsy are the hypomotor seizures, usually with short duration but very frequent occurrence, usually in the night. Hereby, poor quality of sleep can be expected and this might be associated with a variety of cognitive problems [36]. Furthermore unilateral clonic seizures, tonic asymmetric seizures with preserved consciousness and hypermotor seizures, while not pathognomonic, are specific for FLE [33]. Neuropsychological studies are not all consistent in finding cognitive and behavioral deficits specific for FLE [15]. The heterogeneity in the participants of these studies might obscure these results, whereby age seems to be an important variable that could influence cognition in pediatric epilepsy. Hernandez [37] found that preadolescent children with FLE have more difficulties than older children on tests for EF and motor coordination. The developmental stage of the cognitive function in question at the time of seizure onset can also influence the nature of cognitive impairment, with skills in a critical phase of development being more vulnerable to disruption than those in a stable developmental phase [38].

Executive functions

Executive function (EF) commonly refer to deliberate, top-down neurocognitive processes involved in the management of a variety of cognitive processes [39] to engage in independent, purposive, goal-directed and self-serving behavior [40] and is associated with academic success beyond intellectual function [41]. Mental set-shifting or cognitive flexibility, working memory and inhibition are the most well-known [39,42] and have been labelled as ‘cool’ cognitive functions, in which reasoning plays an important role. In contrast, ‘hot’ affective EF, refer to more intuitive top-down processes that operate in motivationally and emotionally situations [43,44] and is associated with emotional problems. Although hot and cool EFs can be dissociated in lesioned brains, they typically work together as part of a more general adaptive function [44,45]. Different EF components demonstrate various developmental trajectories: age-related improvements seem to occur later as well as more gradually for hot than for cold EF components [45]. Executive dysfunction means having difficulties in handling novel situations outside the domain of some of our ‘automatic’ psychological processes. Deficits in EF are related to multiple problems in daily life concerning general functioning and behavior [46,47] and lower quality of life [48]. Also empirical evidence suggests a link between EF and academic performance and psychological well-being [43].

The exact prevalence of EF deficits in children with epilepsy is unknown, due to the use of various test batteries and the choice of cut-off, but some sort of EF is reported up to 50% in children with epilepsy [49]. There is emerging consensus that the most well-known ‘cool’ EF, being cognitive flexibility, working memory and inhibition, are all related to the prefrontal area [30,50-52]. These EF all mature around 9-12 years [53]. Especially ‘cool’ EF is associated with academic performance, but there is evidence suggesting that also behavorial regulation can be associated with academic skills [55]. Hot EF is consistently associated with

developmental outcomes that heavily regress on this emotional regulation [54].
If aforementioned is added up, children in early adolescence with FLE, are particular vulnerable in developing specific EF problems as well as behavioral disturbances. Therefore, this current thesis will focus on the 'cool' EF on one hand as construed from the concepts of cognitive flexibility, working memory and inhibition on the other hand, whereby the more emotional 'hot' EF will be construed from the concept of behavioral regulation.

Parental stress

Parenting a healthy child, with common stressors throughout development, can be challenging [56]. It is therefore not surprising that childhood chronic illness impacts greatly on the entire support system [57] and adds to the normal stress of parenting. Experiencing parental stress is related to various variables like cognitive [58] and behavioral [56] disturbances of the child, caregiver psychopathology [59] and parenting style [60]. Moreover, parenting stress and child behavior problems have been posited to have a transactional effect on each other across development [61].
Especially in epilepsy, behavioral problems are reported more often compared to other conditions [62]. More specifically it seems that externalizing behavior contributes most to experiencing parental stress [63]. As mentioned above, children with FLE display many of these problems. Moreover, specific medical and lifestyle variables accompanying epilepsy can add extra stress on caregivers [64]. Considering all above, parents of pediatric FLE might be more at risk to develop extra parental stress

AIMS AND OUTLINE OF THIS THESIS

The aims of the studies described in this thesis are based on the learning- and behavioral problems in clinical practice. The general aim of this research is to increase the knowledge of the EF in children with FLE that may underlie these learning- and behavioral problems and get more insight in parental stress in order to develop interventions for this specific group. In the addendum we specify the group of participants.
Despite all studies in children with epilepsy, there still remains many unclarities about the relationship between neuropsychological deficits and FLE in children. This will be studied in the first part of this thesis. It is however equally important to further explore the specific behavioral problems and their relationship with possible executive dysfunction which in turn may lead to parental stress. This is something that will be elaborated on in the second part of this thesis.

To specify, the aims in the present thesis are:

1. Systematically review the empirical literature on the association between executive dysfunction and behavioral and socioemotional problems in children with epilepsy (chapter 2).
2. Investigate which behavioral problems are most experienced by parents and teachers of children with frontal lobe epilepsy (chapter 3).
3. Investigate the relationship between executive functions and behavior in school and at home as reported by teachers and parents of children with frontal lobe epilepsy (chapter 3).
4. Explore parental burden of parents children with frontal lobe epilepsy (chapter 4).
5. Asses if parents and teachers of children with frontal lobe epilepsy report executive function problems in daily life (chapter 3,5,6).
6. Explore the association between reported and tested executive functioning of children with frontal lobe epilepsy (chapter 5,6).
7. Investigate if children with frontal lobe epilepsy have poorer working memory skills than normal controls (chapter 5).
8. Determine if children with frontal lobe epilepsy show deficits in inhibition and mental flexibility (chapter 6).

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Addendum

32 Children were enrolled in the total study with the same inclusion criteria: diagnosis of frontal lobe epilepsy, age range 7 years and 10 months to 12 years, IQ > 70 or school achievement scores above C level (Dutch CITO) in math and language. All children underwent the same neuropsychological assessment. However, some children did not cooperate fully leading to missing data. Parents as well as teachers completed the same behavioral questionnaires. For some children the questionnaire data are missing. In table 1 we specify the group of participants for each study.

Table 1: Participants total study

Chapter (short title)	Participants (N) neuropsychological assessment	Participants (N) CBCL/TRF/NVOS	Participants (N) BRIEF parent/teacher
Chapter 3 (executive and behavioral functioning)	n/a	31/ 31	32/ 30
Chapter 4 (burden parenting)	n/a	31/ n/a /31	n/a
Chapter 5 (working memory)	25-29	n/a	32/ 30
Chapter 6 (cognitive control)	31	n/a	31/ n/a

PART I: BEHAVIOR

CHAPTER 2

Associating executive dysfunction with behavioral and socioemotional problems in children with epilepsy: a systematic review

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Abstract

Introduction
As children with epilepsy may have a number of learning and behavioral problems, it is important that insight into the underlying neurocognitive differences in these children, which may underlie these areas of challenge is gained. Executive function (EF) problems particularly are associated with specific learning abilities as well as behavioral problems. We aim to review systematically the current status of empirical studies on the association between EF problems and behavior and socioemotional problems in children with epilepsy.

Methods
Studies were identified using Pubmed and Web of Science, whilst following the PRISMA guidelines. All studies were assessed for methodological quality and results were summarized descriptively.

Results
After search, 26 empirical studies were identified, most of them of moderate quality. Overall, attention problems were the most reported cognitive deficit in test assessment and the most reported problem by parents. In 54% of the studies, children with epilepsy scored below average compared to controls/normative samples on different aspects of EF. Most studies reported behavior problems, which ranged from mild to severe. Forty-two percent of the studies specifically reported relationships between EF deficits and behavioral problems. In the remaining studies, below average neuropsychological functioning seemed to be accompanied by above average reported behavioral problems.

Conclusions
Cognitive control and attention deficits seem mostly associated with especially externalizing behavioral problems. The epilepsy variables early age at seizure onset and high seizure frequency are important variables in the relationship between EF and behavior. Future research should distinguish specific aspects of EF and take age into account, as this provides more insight on the association between EF and behavior in pediatric epilepsy, which makes it possible to develop appropriate and early intervention.

Introduction

Executive function

Executive function (EF) problems [1-5], as well as behavioral and emotional problems [6-13] are common in children with epilepsy. EF is an umbrella term comprising different cognitive processes and behavioral competencies to engage in independent, purposive, goal-directed and self-serving behavior [14]. These cognitive processes encompass among others, attention, inhibition, initiation of activity, working memory, mental flexibility, planning and organization, and problem solving strategies [15] and is associated with academic performance beyond intellectual dysfunction [16]. Deficits in EF can lead to difficulties in handling novel situations outside the domain of some of our 'automatic' psychological processes. These EF deficits are related to multiple problems in daily life concerning general functioning and behavior [9,17]. Recent literature separates EF in two different groups [18]:

Firstly, the more (meta)cognitive EF, in which reasoning plays an important role. It usually involves conscious control of thoughts and actions without an affective component. This is labeled as 'cool' EF and consists of, for example, planning and organization, inhibition, working memory and mental flexibility. Inhibition, mental flexibility and working memory are three well-established subcomponent processes converging in cognitive control [19]. These are in general frequently related to behavioral problems [19-22]. Problems in these areas can lead to lack of inhibitory control in which the ability to deliberately lower the interference of unwanted stimuli is affected. Also mental inflexibility, while the ability to flexibly adjust behavior to the demands of a changing environment, is often disturbed. Furthermore, working memory problems are often reported, meaning having problems in maintaining and actively manipulate the contents of working memory.

Secondly, there is the so-called 'hot' affective EF, which is associated with emotional problems and comprises among others emotional regulation and self-monitoring. Hot EF has been suggested to include affective cognitive abilities. Disruption of emotional regulation can be caused by poor inhibitory control.

Besides the relation with behavioral problems, 'cool' as well as 'hot' EF are also associated with academic performance and even behavorial regulation on its own is associated with academic skills [23].

EF in children with epilepsy

The prevalence of executive dysfunction in children with epilepsy is unknown, due to the use of different test batteries and the choice of cutoff [6]. As optimal cutoffs are debatable [24], some studies use a cutoff of two standard deviation (SD) to consider a result as a 'true' deficit, which is also frequently advised by the manual, while other studies also consider scores below 1,5 SD as a deficit scores, which often is viewed (only) as below average. Some degree of EF problem is, however, reported in up to 50% [25]. Specifically, the aforementioned cognitive control problems are identified in children with epilepsy. It has been reported that children with epilepsy, experiencing executive dysfunction have poor quality of life [26-28] and comorbid behavioral problems are reported in up to two-thirds [9].

From a neurological perspective, epilepsy can interfere with the development of brain networks underlying cognition and behavior [29-32]. In general, the underlying epilepsy pathology and a bidirectional relationship between behavioral and cognitive disorders and epilepsy have been suggested (figure 1) [33-37]. With skills in a critical phase of development being more vulnerable to disruption than those in a stable developmental phase [38], age at seizure onset may influence the nature of cognitive impairment.

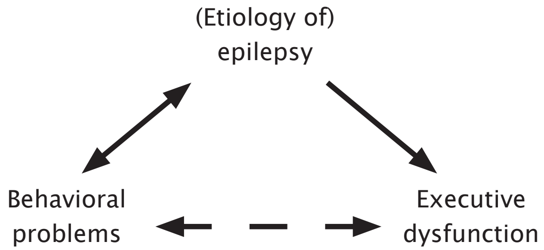

Figure 1: bidirectional relationship

It is suggested that early age at seizure onset results in greater EF impairment [39-41]. Law, Smith and Widjaja [42] found that younger age at seizure onset is related to damage thalamocortical pathways, which is seen as a potential mechanism of EF impairment. Bell & Wolfe [43] argued that in children with epilepsy, early impairment might affect reorganization in the brain. Cognitive delays in children with epilepsy may be seen as a consequence of long-term developmental changes. The development of EF continues throughout adolescence, while early adolescence is seen as a period of significant maturation for the brain's functional architecture.

Epileptic activity in this important timeline of brain maturation might put a child more at risk for developing executive dysfunction and adjoining academic and (social) behavioral problems. High seizure frequency is for instance linked to (subjective) cognitive impairment [40,44) and EF deficits [45] while seizures starting subcortically and propagating upward through subcortical structures critical for EF. High seizure frequency is also suggested to play a role in the perceived quality of life and development of depression [46]. This suggests that high seizure frequency on its own may lead to poor EF as well as depressive complaints, both known to lower the quality of life and impact behavior. This might be an important variable to take into account when considering EF development and behavioral problems. Epilepsy localization can play an important role in the development of EF problems. EF was, until recently, recognized as an isolated frontal lobe

function. Thus, in the context of this review it might be expected that EF will be most affected in children with frontal lobe epilepsy as reported previously [e.g. 47]. Growing evidence, however, suggests that the prefrontal cortex is part of a broader functional system, which involves other brain regions and networks [48,49]. Although the prefrontal cortex undoubtedly still plays a major role in EF across development, and prefrontal disruption is indeed sufficient to produce EF problems, it has to be considered within the context of a constant interplay with other key nodes in these networks [49]. Dysfunction of the prefrontal cortex is not the only requirement for executive dysfunction as multiple neural networks are involved and dysfunction in any can result in executive impairment [50,51]. Some studies have shown executive (dys)function beyond the frontal lobe [52-54] and there is also growing evidence for a fronto-parietal network [55-57].
While several studies have identified EF deficits and behavioral problems in children with epilepsy, few have examined whether there is a direct association between both. These few studies suggest that executive dysfunction is a risk factor for developing behavioral and psychiatric problems. Evidence from studies in developmental psychopathologies also seem to point towards a relationship between EF problems and behavioral problems [58-60]. While EF deficits are common in a wide variety of childhood disorders, attention-deficit hyperactivity disorder (ADHD) is the most common childhood disorder, which frequently presents with EF impairment, as well as associated academic, social, and functional difficulties [61]. There is a high rate of comorbid ADHD in epilepsy [62]. MacAllister et al [40] suggests that the high rate of attention problems and executive dysfunction are responsible for this increased incidence of ADHD in children with epilepsy. Indeed, the underlying neuropsychological endophenotype of ADHD in those with epilepsy appears to differ from those with ADHD and no seizures. Firstly, children with seizures are more frequently diagnosed with the inattentive subtype of ADHD, while in the general population ADHD of the hyperactive subtype is more common. Children with epilepsy and ADHD perform worse on a variety of EF tasks and have lower IQ scores compared to children with ADHD and no seizures. Epilepsy variables seem unrelated to a ADHD diagnosis in a few studies, however, another study [45] highlighted that in children with seizures, attentional impairment is secondary to many factors, including not only the underlying brain pathology that causes both the cognitive deficits and epilepsy, but also the seizures themselves, which cause ictal and postictal symptoms. There are, however, few studies comparing the performance on several EF tasks of children with ADHD without seizures to that of children with seizures and ADHD.

Social functioning

EF also encompasses behaviors necessary for social interaction, such as initiation, self-monitoring, and self-regulation [14], which may be essential for adequate social functioning [63]. To engage in successful social interaction it is essential to have good social cognition skills. This encompasses four different domains globally: emotional perception, social perception, attribution style and Theory of Mind (ToM) [17]. These domains are crucial for successful communication and interpersonal relationships for social functioning. ToM is the ability to understand the thoughts, intentions, beliefs and emotions of others and oneself and is comprised of component processes, including cognitive perspective taking (cognitive ToM) and emotional understanding (affective ToM). These have different developmental trajectories [64].

In daily life, EF skills such as self-monitoring and inhibitory control might be necessary to understand the mental states of oneself and others. Self-monitoring might be required for self-awareness, and this is a prerequisite for Theory of Mind (ToM). The ability to inhibit and shift perspectives seems necessary to understand the mental states of others. Besides, evidence provides support for the notion that ToM and EF are at least partially separable in the brain, but also demonstrate considerable overlap [65].

It is suggested that social cognition in general is correlated with performance on different aspects of classic EF [17,66]. Of all the theory of mind abilities, the most assessed in this regard has been the understanding of false belief, which in general terms has been positively associated with flexibility, inhibition and working memory (being all part of cognitive control), but not planning [67]. Impairments in ToM and EF are associated with a range of neurodevelopmental and psychiatric conditions across the lifespan, while an association between EF and social cognition problems in autism spectrum disorders and ADHD is also established [66].

This could indicate that impairments in EF might underlie or account for impairments in ToM and social competence in children with generalized epilepsy [68]. This could imply that children with epilepsy with good EF also have good social cognition skills and that children with epilepsy with EF problems also encounter social cognition problems and that social functioning is affected. Epilepsy is in general associated with widespread social difficulties: reduced social competence, poor social skills and social communication deficits [69]. Impaired ToM, as related to impaired EF, might underpin these social difficulties in children with epilepsy [69] and can have many implications in daily life [70].

Research questions

Overseeing it all, children with epilepsy suffering from EF problems seem to be at risk in developing academic and socioemotional behavioral problems [28]. The purpose of this review is to review systematically studies concerning EF and socioemotional behavior in pediatric epilepsy with a focus on their association as tested with standardized tests and well-established questionnaires. This knowledge is essential to develop appropriate interventions for this specific patient group, including parenting support.

To shed more light on this issue, this review will address the following main research question:
Is it possible to identify specific EF skill areas that differentially relate to behavioral or social-emotional problems in children with epilepsy? To answer this question more specifically, additional research questions are:

a. Which EF deficits can be identified in relation to behavioral functioning?
b. Which social cognition problems can be identified in relation to EF and behavioral functioning?
c. Can EF deficits be associated with psychiatric comorbidity?

To answer this adequately, this review will also, although not thoroughly, address questions concerning the presence of EF deficits and behavioral problems in children with epilepsy. This review also aims to identify epilepsy variables that can be identified as important (possible causal) factors in the delayed development of EF.

Methods

Review protocol

The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines were followed [71]. It consists of a four-phase flow diagram and a 27-item checklist divided into 8 sections (title, abstract, introduction, methods, results, discussion, funding). It clearly describes which items to include when reporting a systematic review or meta-analysis.

Search and selection process

We searched Pub-Med (National Center for Biotechnology Information; NCBI; http://www.ncbi.nlm.nih.gov/pubmed/) and Web of Science up to May 2020 using a wide range of keywords, in different combinations. Search terms included (1) a broad range of relevant terms for EF, (2) terms relevant for behavior and (3) terms to describe epilepsy or seizures, all searched for in title and abstract. To narrow the search, the variable child with its different synonyms was added. A complete list of search terms is provided in appendix A.
After all double hits were deleted, studies were screened for relevance based on titles and abstracts. The remaining studies were screened full text. Finally, reference sections of empirical studies and reviews were inspected for other relevant articles that had not yet been identified.
A second search was conducted on May 4th 2020 to identify studies published between June 2018 and May 2020. The additional search terms “shift” and “cognitive control” were used and combined with the text variables.

Criteria for inclusion

Studies included in the current review:

I. reported original empirical research (i.e., not reviews, meta-analyses, editorials or letters);
II. included children or adolescents with epilepsy;
III. reported data (M, SD) about children with epilepsy separately, if other groups were included;
IV. assessed EF with a performance-based measure (table 3) validated for neuropsychological assessment (e.g. Wisconsin Card Sorting Test (WCST) [72]; Stroop Color Word Test (SCWT) [73]; Delis-Kaplan Executive Function System (D-Kefs) [74]. Or EF was assessed with the Behavior Rating Inventory of Executive Function (BRIEF) [75] an 86-item proxy questionnaire which assesses executive function behaviors in the school and home environments or the second edition the BRIEF-2 (published in 2015, encompassing 63 items);
V. assessed behavior or social-emotional functioning with a validated and reliable questionnaire (e.g. Child Behavior Checklist (CBCL) [76]; Behavior Assessment System for Children (BASC) [77]);
VI. epileptic encephalopathies (such as Continuous Spikes and Waves during Sleep, Landau Kleffner Syndrome, Dravet Syndrome) were excluded.

Studies were only included if outcome data were provided on the specific relationship between variables of EF and behavior or reported about both in the same study. Only studies in English published in peer-reviewed journals were included.

Studies were judged on their quality, using the Newcastle-Ottawa Scale (NOS) [78], which was based on its applicability for studies with case-control, cohort and cross-sectional designs and validity seems good [79]. This tool provides a checklist covering three domains (selection, comparability and exposure) with 9 items in total and provides a standardized method to weigh items. We rated the quality of the studies (good, fair and poor) by awarding stars in each domain following the guidelines of the NOS. As seen in table 1, a “good” quality score required 3 or 4 stars in selection (representativeness of the cohort), 1 or 2 stars in comparability (adjusted for confounders or matched sample), and 2 or 3 stars in exposure (ascertainment of exposure). A “moderate” quality score required 2 stars in selection, 1 or 2 stars in comparability, and 2 or 3 stars in exposure. A “poor” quality score reflected 0 or 1 star(s) in selection, or 0 stars in comparability, or 0 or 1 star(s) in exposure

Table 1: Quality assessment based on the Newcastle-Ottawa Scale [78]

Study	Selection (max 4 stars)	Comparability (max 2 stars)	Exposure (max 3 stars)
High quality			
Ayaz et al., 2013 [9]	★★★	★★	★★★
Conant et al., 2010 [79]	★★★★	★★	★★★
Hernandez et al., 2003 [80]	★★★★	★★	★★★
Hoie et al., 2008 [81]	★★★★	★★	★★★
Lew et al., 2015 [82]	★★★★	★★	★★★
Parrish et al., 2007 [83]	★★★★	★★	★★★
Raud et al., 2015 [84]	★★★★	★★	★★★
Schaffer et al., 2015 [85]	★★★★	★★	★★★
Seidel & Mitchell, 1999 [86]	★★★	★★	★★★
Stewart et al., 2018 [67]	★★★★	★★	★★★
Moderate quality			
Alfstad et al., 2016 [6]	★★	★★	★★★
Baum et al., 2010 [87]	★★	★★	★★★
Braakman et al., 2012 [88]	★★	★	★★★
Burns et al., 2018 [97]	★★	★★	★★★
Giordani et al., 2006 [90]	★★	★★	★★★
Hessen et al., 2018 [2]	★★	★★	★★★
Kavanaugh et al., 2015 [98]	★★	★★	★★★
Modi et al, 2019 [25]	★★	★★	★★★
Operto et al., 2020 [92]	★★	★★	★★★
Piccinelli et al., 2010 [93]	★★	★★	★★★
Sarco et al., 2011 [99]	★★	★	★★★
vandenBerg et al., 2018 [95]	★★	★★	★★★
Williams et al., 1998 [96]	★★	★★	★★★
Low quality			
Bhise et al., 2009 [89]	★★		★★★
Kwon et al., 2012 [91]	★★		★★★
Triplett & Asato, 2015 [94]	★★		★★★

Note. 'Selection' concerns the representativeness of the exposed cohort. It is assessed with 4 items (adequate case selection, representativeness of the cases, selection of controls, definition of controls). 'Comparability' refers to that either exposed and non-exposed individuals must be matched in the design and/or confounders must be adjusted for in the analysis and is assessed with 1 item. 'Exposure' refers to the ascertainment of exposure. This is assessed with 3 items (ascertainment of exposure, same method of ascertainment for cases and controls, non-response rate).

Results

Of the 3521 papers identified in the search, a total of 26 studies met the inclusion criteria (see figure 2). Quality assessments for each study are summarized in table 1. These results show moderate quality for most studies, in a large part due to the lack of control groups and/or lack of sufficient correction for biases. Sufficient quality concerning the guidelines of the NOS was found in ten studies [9,68,80-87].

Study characteristics

Table 2 shows the characteristics of included studies. Twenty-six studies included 1957 children in total. 573 children had generalized epilepsy (GEA) (11 juvenile myoclonic epilepsy (JME); 129 childhood absence epilepsy (CAE); 433 other/unspecified). 1279 had focal epilepsy (FE) (197 frontal lobe epilepsy (FLE); 100 temporal lobe epilepsy (TLE); 346 benign epilepsy with centrotemporal spikes (BECTS); 485 other/unspecified). 105 children were not classified neither as GEA or FE, in the table classified as other. The mean age ranged from 8 to 14 years with equal distribution of males and females. Ten (38%) studies used a control group, which were all the high-quality studies [9,68,80-87].

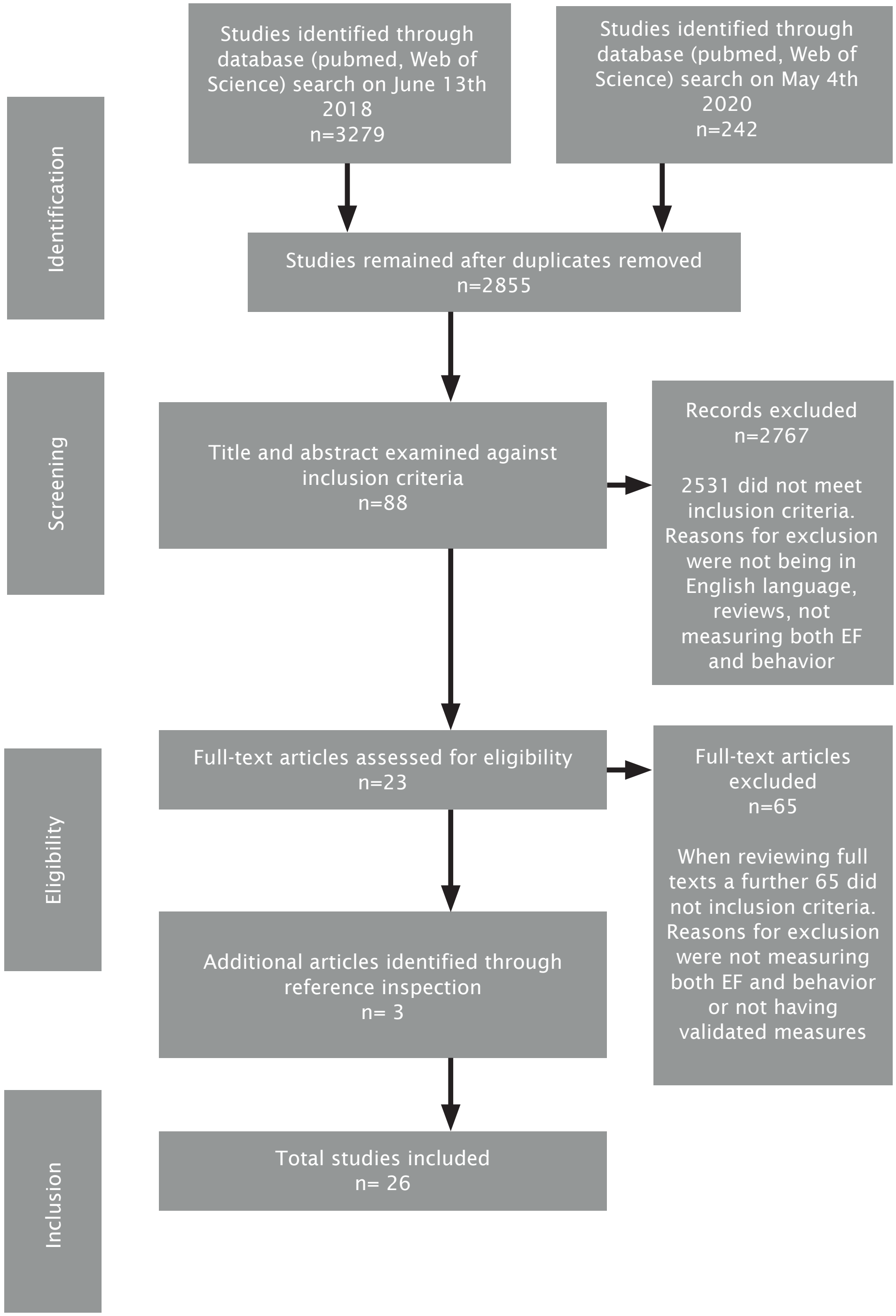

Figure 2: outline of literature search

Table 2: Study descriptions

Study	Aims	Study design	Participants (m:f)	Age M (SD) years
Alfstad et al., 2016 [6]	Explore risk factors for psychiatric disorders with emphasis on executive dysfunction	Case-control	52 FE (13 TLE, 19FLE, 12 BECTS, 8 Unspecified), 49 GEA (17 CAE, 7 JME, 25 other) (49:52)	14.1(4.1)
Ayaz et al., 2013 [9]	Assess behavioral problems, psychiatric disorders and neurocognitive evaluation focused on frontal lobe functions	Case-control	31 BECTS (18:13)	10.17 (1.61)
Baum et al., 2010 [88]	Investigate the unique contributions of retrospectively assessed infant temperament and neuropsychological functioning 3 years after seizure onset and investigate the potentially moderating effect of neuropsychological functioning on the infant temperament-behavior relationship	Cross sectional	148 FE, 81 GEA (114:115)	9.5(2.6)
Bhise et al., 2009 [90]	To assess baseline function with respect to new learning, attention and memory.	Cross sectional	34 FE, 23 GEA (15:42)	10.1(2.9)
Braakman et al., 2012 [89]	Assess cognitive skills and behavior	Cross sectional	71 FLE (46:25)	10.75(2.8 months)
Burns et al., 2018 [98]	Assess cognitive performance and behavioral symptoms	Case-control	98 FE (58 TLE, 28 FLE, 12 unspecified) (51:48)	10.7(2.6)
Conant et al., 2010 [80]	Examine neuropsychological functioning	Case-control	16 CAE (5:11)	8(1.3)
Giordani et al., 2006 [91]	To understand cognitive and behavioral co-morbidities in a relatively large sample of children with BECTS	Cross sectional	200 BECTS (115:85)	8.2(2.2)
Hernandez et al., 2003 [81]	Explore whether attention, memory and behavior would be more affected in children with FLE than in children with other types of epilepsies	Case-control	32 FE (16 FLE, 8 TLE), 8 GEA (20:12)	11.15 (2.89)-12.44 (2.81)
Hessen et al., 2018 [2]	Explore factors associated with executive problems for patients with epilepsy in children	Cross sectional	47 FE (14 TLE, 20 FLE, 12 BECTS, 1 other), 50 GEA (4 JME, 18 CAE, 28 other) (44:53)	14(2.4)
Hoie et al., 2008 [9]	To investigate the combined burden of cognitive, EF, and psychosocial problems in children with BECTS	Cross sectional	84 FE, 62 GEA, 16 other (99:63)	10.2(1.9)
Kavanaugh et al., 2015 [99]	Examine clinical and demographic risk factors associated with parent-rated emotional-behavioral and EF	Case-control	33 CAE, 64 FE, 55 other (70:82)	10.69(3.4)
Kwon et al., 2012 [92]	Assess the cognitive and other neuropsychological profiles	Cross sectional	23 BECTS (23 FE) (13:10)	9(1.6)
Lew et al., 2015 [83]	Establish whether deficits in social cognition are present and whether any relation exist between social cognition, communication and behavior measures	Case-control	27 FE (7 BECTS, 7 TLE, 5 FLE, 8 other), 20 GEA (5 CAE, 15 other) (20:27)	11.6 (2.6)-11.8 (2.2)

Table 2 continued

Study	Aims	Study design	Participants (m:f)	Age M (SD) years
Modi et al., 2019 [25]	To identify (EF) phenotypes in youth with epilepsy	Cross sectional	115 FE, 88 GEA, 34 other (105:132)	11.2(3.9)
Operto et al., 2020 [93]	To evaluate EF and the emotional-behavioral profile in adolescents with focal drug-resistant epilepsy at baseline and after 6 and 12 months of add-on treatment with Perampanel	Case-control	37 (FE) (22:15)	13.78(1.6)
Parrish et al., 2007 [84]	Examine the association between the BRIEF and performance on the D-KEFS. Determine whether the BRIEF or CBCL is a stronger predictor of performances on the D-KEFS	Cross sectional	30 FE, 23 GEA (31:22)	11.6(3.6)
Piccinelli et al., 2010 [94]	Study neuropsychological functions and to identify factors associated with cognitive impairment	Cohort	20 FE (5 FLE, 10 BECTS, 5 other), 23 GEA (19 CAE, 4 other) (21:22)	10.4(3.1)
Raud et al., 2015 [85]	Examine associations between sociocognitive skills and neurocognitive performance	Case-control	25 FE, 10 GEA (15:20)	10.46 (1.85)
Sarco et al., 2011 [100]	Evaluate associations between the EEG spike frequency index and parental ratings of psychosocial adjustment and EF	Cross sectional	22 BECTS (11:10)	9.38
Schaffer et al., 2015 [86]	Assess memory, psychosocial function and the relationship between these two domains	Case-control	19 BECTS, 11 GEA, 3 CAE (16:17)	10.88 (1.52)
Seidel & Mitchell, 1999 [87]	Investigate the cognitive and behavioral effects of carbamazepine	Case-control	10 BECTS (6:4)	9.7(2.0)
Stewart et al., 2018 [68]	To examine cognitive and affective ToM and social competence in children and adolescents with GGE	Cross sectional	22 GEA (8:14)	12.82(2.82)
Triplett & Asato, 2015 [95]	Pilote a computerized cognitive battery and behavioral questionnaire	Cross sectional	28 GEA, 10 FE (19:19)	12.4(2.2)
vandenBerg et al., 2018 [96]	To examine relationships between FLE and executive and behavioral functioning reported by parents and teachers	Cross sectional	32 FE (FLE) (18:14)	9.2(1.6)
Williams et al., 1998 [97]	Examine patterns of neuropsychological function	Case-control	56 FE, 23 GEA (18 CAE, 5 other) (42:37)	10.2(2.11)

Note BECTS=benign childhood epilepsy with centrotemporal spikes, CAE=childhood absence epilepsy, EF=executive function, FE=focal epilepsy, FLE=frontal lobe epilepsy, GEA=generalized epilepsy, JME=juveniele myoclone epilepsy, TLE=temporal lobe epilepsy

Table 3 provides an overview and description of the applied instruments in the included studies. Because of the scope of this review only the instruments that were used in the studies to assess EF and behavior are described.

Study outcome

Used tools

As shown in table 3 there was much heterogeneity among the studies in the tests and questionnaires used, and also in the cutoff points used in the assessments. Some studies used a conservative 2 standard deviation (SD) below the mean to indicate deficits, while other studies used 1.5 SD below the mean. In table 4 the results of children with epilepsy compared to a normative sample or control group is described. Eighteen studies used the Achenbach scales (Childhood Behavior Checklist (CBCL) and/or Teacher Report Form (TRF)) [9,68,80,81-84,86,88-97] to assess emotional and behavioral problems. Seven studies used the BRIEF [2,25,84,96,98-100] to assess EF as reported by parents. Furthermore, a variety of other questionnaires were only used in one (e.g. Social Communication Questionnaire (SCQ)) [85] or up to four studies (Behavior Assessment System for Children (BASC) [25,98-100], Strengths and Difficulties Questionnaire (SDQ) [2,6,68,95]. EF was tested with a broad range of tools. Some studies used a composite EF score, while others measured different aspects of EF. The Wisconsin Card Sorting Test (WCST) [9,80,82,92,94,97,98] and (parts of the) Delis-Kaplan EF System (D-KEFS) [2,6,84,98] were the most frequently used tests to assess executive functioning. Different Continuous Performance Tasks (CPT) [81,87-89;94,97) were used to assess attention. The Wide Range Assessment of Memory and Learning (WRAML) includes working memory and was the most used test to assess memory [80,87,88,90,91,97].

Table 3: Measure descriptions

Measure	Description	Psychometric characteristics
Executive function		
Behavior Rating Inventory of Executive Function (BRIEF)	A standardized questionnaire assessing executive functions in children and adolescents, it has a parent and teacher form and a self-report.	Reliability (test-retest and internal consistency) and validity (convergent, discriminant, predictive) are satisfactory [75].
Conner's Continuous performance test (CPT)	Visual paradigm for the evaluation of attention and response inhibition component of executive control.	Adequate reliability (split-half, test-retest) [101].
Color-Word Inference Test (CWIT) of the Delis-Kaplan Executive Function System (D-Kefs)	Version of the Stroop Test that measures inhibition of verbal responses through naming dissonant ink colors.	The D-KEFS provides a valid and reliable means to measure individual executive functioning [102].
Freedom from distractibility (FD)	A factor of the WISC III comprising Arithmetic and Digit Span.	FD is not a reliable or valid index of attention [103].

Table 3 continued

Measure	Description	Psychometric characteristics
Gordon Diagnostic System Vigilance Task (GDS)	Continuous performance test that is well established as a measure of attention.	Convergent and predictive validity are adequate [104]. Adequate test-retest reliability [105].
Kim's frontal executive neuropsychological test (K-FENT)	An executive function testbattery composed of several subtests: Stroop Test, Figural Fluency Test, Word Fluency Test, and Auditory Verbal Learning Test.	No studies were found on the psychometric properties of this instrument
A Developmental Neuropsychological Assessment (NEPSY)	A multidomain neuropsychological battery for children.	Validity is adequate [106]. Reliability and validity ranges from low to high on different subtests [107].
Stroop Color and Word Test (SCWT)	Well-known test which measures the ability to resist interference	Adequate test-retest reliability in healthy subjects [108]. Relatively high ecological validity [109].
Trail Making Test (TMT)	Widely used test to measure cognitive flexibility	The B/A ratio of performance in the TMT provides an index of executive function [110]. It has a comprehensive set of norms [111].
Tower of London (ToL)	Well-known test which measures planning ability	Adequate psychometric properties for adults [112]. Reliable instrument for both clinical and non-clinical child samples aged 6 to 13 years [113].
Wisconsin Card Sorting Test (WCST)	Widely used test to measure cognitive flexibility	High interrater reliability [114], adequate validity and low retest reliability [115]. In a pediatric sample, adjusted cutoffs ensure good specificity, but with low or variable sensitivity [116].
Wide Range Assessment of Memory and Learning (WRAML)	A broad-based memory battery that provides a flexible measure of memory functioning and learning, including working memory.	There is considerable inter- and intra-individual performance variability across the nine subtests. A high base-rate of performance variability was observed across the four index scores [117].
Behavior		
Behavior Assessment System for Children (BASC)	Five measures designed to gather information about a child or adolescent from a variety of sources	Reliability is quite high, validity is adequate [77]. The BASC has diagnostic and clinical utility in assessing behavior problems in pediatric epilepsy [118].
Child Behavior Checklist (CBCL), Teacher Report Form (TRF)	A behavioral questionnaire filled in by parents and teachers. 8 Subscales comprises two factors: internalizing and externalizing behavior.	Good validity and reliability [76]

Table 3 continued

Measure	Description	Psychometric characteristics
Children's Communication Checklist (CCC-2)	Parental checklist on communication abilities of children	Adequate discriminant validity, good interrater agreement [119].
Children's Depression Inventory (CDI)	A screener for depressive symptoms in children and adolescents	Adequately reliable and highly valid in terms of assessing depressive symptoms [120]. Psychometrics are similar for children with chronic diseases compared with typically developing children [121].
Kutcher Adolescent Depression Scale (K-ADS)	A self-rated depression scale for adolescents	A reliable, sensitive and valid measure [122].
Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime Version (K-SADS PL)	A semi-structural integrated parent-child interview according to DSM criteria	Excellent interrater reliability, fair test-retest reliability, adequate concurrent validity [123]. Convergent and divergent validity was supported for all categories [124].
Pediatric Quality of Life (PedsQL)	A childs self-report and a parents proxy report to measure health related QOL	Adequate reliability and validity [125]. It demonstrates excellent internal consistency reliability, discriminant, concurrent, and construct validity in youth with epilepsy [126].
Parents Rating Scale (PRS)	Questionnaire intended to measure emotional and behavioral skills	High test-retest reliability, adequate convergent validity [127].
Readiness for Integrated Care Questionnaire (RICQ)	An Instrument to Assess Readiness to Integrate Behavioral Health and Primary Care	No studies were found on the psychometric properties of this instrument.
Social Communication Questionnaire (SCQ)	Parent report questionnaire on social communication.	Adequate validitiy and reliability is generally satisfactory [128].
Strenghts and Difficulties Questionnaire (SDQ)	Brief measure of prosocial behavior and psychopathology of 3-16-year-olds that can be completed by parents, teachers, or youths.	Internal consistency, test-retest reliability, and inter-rater agreement are satisfactory for the parent and teacher versions [129].
Social Skills Ratings System (SSRS)	One of the most widely used measures of children's social behaviors	High internal consistency and moderately high validity indices [130].
Theory of Mind Inventory (TOMI)	Ratingscale for caregivers designed to tap a wide range of social cognitive understandings of their children.	High reliability and adequate validity [131].

Do children with epilepsy exhibit EF deficits as well as behavioral problems?
In 54% of the studies, children with epilepsy scored overall lower than controls/normative samples on different aspects of executive function (including stand-alone measures of attention, working memory, inhibition and sociocognition) [6,25,68,80,81-85,90,93-96]. However, the majority of these studies failed

to show significantly lower results exclusively for EF and six studies reported no lower scores at all [2,88,91,92,97,98]; this included tested EF as well as parent reported EF. Memory problems [81,86,87,89,91,95] and attention problems [80,81,85,90,95,99] were the most frequently reported cognitive problems. Attentional problems were also most frequently reported by parents on behavioral questionnaires. There has been little study of social cognition in relation to EF [68,83,85].
Behavioral problems were found in 20 (77%) studies [6,9,25,68,80-86,89,91,93-97,99,100] varying from (mild) attentional to aggression problems. Internalizing behavioral problems were reported to the same extent as externalizing behavioral problems. Somatic complaints as well as anxiety and mood problems, which are in general reported frequently in epilepsy, were reported to a lesser extent [80,81,91-93,96,97,100].

Which epilepsy variables can be identified as important (possible causal) factors?
Epilepsy variables might play an important role in the emergence of EF problems. These variables might cause problems to persist or worsen. In general, the epilepsy variables most often reported are age at seizure onset, duration of epilepsy, seizure frequency, seizure types and number of antiseizure medications (ASMs). Epilepsy variables were reported in 20 (77%) studies. Table 5 shows relevant epilepsy variables.
As described, the prefrontal cortex plays a major role in the development of EF. Differentiating between epilepsy types may be important. From a cognitive perspective two studies reported that children with GEA performed lower on cognitive tasks than children with FE [85,90], whereas another study reports FE performing lower on an inhibition measure compared to GEA [84]. One study [81] showed that children with FLE had more impulsivity and behavioral regulation problems and that they were more perseverative and more susceptible to interference compared to children TLE and GEA. Other studies including children with GEA and FE reported no differences in cognitive tasks. All in all comparing generalized epilepsies (GEA) with focal epilepsies (FE) or different foci showed small and not conclusive differences between these two different epilepsies and foci. For behavioral problems, most studies showed no difference between children with GEA or with FE. Two studies showed that those with GEA displayed more behavioral problems than those with FE [80,90].
The epilepsy variables most associated with different behavioral problems and/or cognitive deficits were early age at onset in 5 studies [2,6,9,85,96] and high seizure frequency in 5 studies [9,81,89,99,100]. However, four studies reported these variables not to be of influence [6,68,89,93]. Furthermore, duration of epilepsy is reported in relation to cognition [85] and behavior [93,96], while two other studies reported no association [68,89]. Five studies reported the effect of ASM specifically [2,6,93,94,98]. Newer ASMs, such as perampanel, oxcarbazepine and lamotrigine seem to have fewer cognitive and behavioral side effects than older ASMs such as valproate [98] and, to a lesser extent, carbamazepine. One study reported specifically about negative effects of Topiramate when evaluating EF [98].

Table 4: Study results

Study	Neuropsychological tests*	Questionnaires*	Main outcome**	Test results compared[a] to norm scores or controls**	Questionnaires compared[a] to norm scores of controls**
Alfstad et al., 2016 [6]	Verbal intelligence: WASI Delayed memory: RAVLT, RCFT EF: D-KEFS	Behavior: SDQ K-SADS-PL	Executive dysfunction is an independent risk factor for psychiatric comorbidity. Vice versa: having a psychiatric disorder could also be a predictor of EF difficulties.	Executive score: Psychiatric disorder < without disorder Verbal ability, memory: Psychiatric disorder = without disorder	Prevalence of psychiatric disorders: 43,6%
Ayaz et al., 2013 [9]	General Ability: WISC-R EF: WCST SCWT	Behavior: CBCL K-SADS-PL	RE had negative effects on neurocognitive functions, behaviors and psychological health, not specific for frontal lobe functions. There was a marked effect on only attention.	All: Epilepsy=controls	Externalizing problems: Epilepsy<controls Internalizing problems: Epilepsy=controls 66% psychological disorder
Baum et al., 2010 [88]	General Ability: K-BIT Language: CELF-3 CTOPP Attention: CPT-2 Processing Speed Coding and symbol search of WISC-III	Behavior: RICQ TRF	Negative temperamental characteristics predicted behavior problems three years after seizure onset. 'Resistant to control' temperaments were predictive of total behavior problems. Children, who scored lower on EF, were at greater risk for behavior problems.	All: Epilepsy=norm	Behavior: Epilepsy=norm

Table 4 continued

Study	Neuropsychological tests*	Questionnaires*	Main outcome**	Test results compared[a] to norm scores or controls**	Questionnaires compared[a] to norm scores of controls**
Baum et al., 2010 [88] continued	Memory: WRAML EF: WCST				
Bhise et al., 2009 [90]	General ability: KAIT Memory: WRAML CVLT Attention: SCWT Test of Variables of Attention EF: TMT Motor: Grooved Pegboard Tests	Behavior: CBCL Depression/Anxiety: CDI Revised Children's Manifest Anxiety Scale.	Overall lower scores. Evidence for an intrinsic weakness in attention associated with epilepsy of all subtypes. Children with GEA performed lower on most tasks and were rated higher on (social) behavior problems in comparison to children with FE	Attention: Epilepsy<norm Other Epilepsy = norm	Epilepsy = norm
Braakman et al., 2012 [89]	General Ability: WISC-III Memory: Fepsy Recognition 15-WT Visual-spatial functions: RCFT	Behavior: CBCL TRF	Children with FLE show a broad range of cognitive (broader than the typical frontal functions) and behavioral impairments and a global decline of IQ scores.	Visual spatial, memory (learning new information), psychomotor speed, alertness: FLE<norm Attention, memory (recall information):	Internalizing, attention, anxiety (parents): FLE<norm Attention, aggression (teacher): FLE<norm

Table 4 continued

Study	Neuropsychological tests*	Questionnaires*	Main outcome**	Test results compared[a] to norm scores or controls**	Questionnaires compared[a] to norm scores of controls**
Braakman et al., 2012 [89] Continued	Beery Psychomotor speed and alertness: Fepsy finger tapping, reaction time, CVST Attention: SCWT Bourdon-Vos test School achievement: Tempotest			FLE=norm	Other (parent and teacher): FLE=norm
Burns et al., 2018 [98]	General Ability: WISC-IV EF: D-KEFS	EF in daily life: BRIEF Behavior: BASC-2 PRS	In general newer AEDs are associated with less cognitive side effects than Valproate, with the exception of Topiramate.	Working memory: Epilepsy=norm D-KEFS: Epilepsy=norm	EF: Epilepsy=norm Behavior: Epilepsy=norm
Conant et al., 2010 [80]	Achievement: WRAT-3 Memory: WRAML Fine motor speed: Finger tapping Processing speed: WISC-III	Behavior: CBCL	There are specific weaknesses in executive and related functions in 6- to 10-year old children with CAE. Most marked are aspects of novel problem solving and complex motor control. Also elevated levels of social dysfunction and behavioral inhibition problems.	Attention/behavioral inhibition, letter fluency, EF, complex motor control: Epilepsy < controls Achievement, memory, fine motor speed, processing speed: Epilepsy = controls	Withdrawn, social problems, thought problems: Epilepsy < controls Anxious/depressed, somatic complaints: Epilepsy = controls

Table 4 continued

Study	Neuropsychological tests*	Questionnaires*	Main outcome**	Test results compared[a] to norm scores or controls**	Questionnaires compared[a] to norm scores of controls**
Conant et al., 2010 [80] continued	Complex motor control: KABC VMI motor timing EF: ToL WCST Verbal fluency: COWA Categoral Fluency Attention/behavioral inhibition: GDS Attention, delinquent behavior, agressive behavior scales of CBCL				
Giordani et al., 2006 [91]	Verbal PPVT–III Memory: WRAML Motor: Purdue Pegboard	Behavior: Conners' parent rating scale	Cognitive skills within average limits. Relative weakness in attentions skills.	All tasks: Epilepsy=norm	Psychosomatic and learning: Epilepsy < norm Conduct, impulsive/hyperactive, anxiety, hyperactivity: Epilepsy = norm

Table 4 continued

Study	Neuropsychological tests*	Questionnaires*	Main outcome**	Test results compared[a] to norm scores or controls**	Questionnaires compared[a] to norm scores of controls**
Hernandez et al., 2003 [81]	General Ability: PS and FD of WISC-III Attention: CPT Memory: CVLT, RCFT	Behavior:| CBCL	All groups impaired on attention and memory. Children with FLE were more impaired than children with GEA en TLE, which suggest that this group is at greater risk of developing school problems. Children aged 8-12 with FLE were significantly more impaired on several tasks. Deficit in attention and working memory were the most persistent problems of the older children with FLE.	All tasks: FLE < control TLE,GEA < control	Thought, attention: FLE < control TLE,GEA = control Other: FLE,TLE,GEA = control
Hessen et al., 2018 [2]	General Ability: WASI EF: D-KEFS	EF in daily life: BRIEF Behavior: SDQ	Parent-reported everyday executive dysfunction best correlated with tested executive dysfunction and vice versa. Male gender showed the strongest association with the BRI of the BRIEF. High level of psychiatric problems contributes to a high level of everyday behavioral executive dysfunction.	EF: Epilepsy=norm	EF: Epilepsy=norm Behavior: Epilepsy=norm
Hoie et al., 2008 [9]	General Ability: RAVEN EF: ITPA VMI 10 Unrelated words Word fluency test WCST WISC-R coding	Behavior: CBCL TRF	Mild cognitive, EF problems and/or psychosocial problems were common in children with BECTS with normal intellectual functioning.	All: Epilepsy<controls	Behavior: Epilepsy<controls

Table 4 continued

Study	Neuropsychological tests*	Questionnaires*	Main outcome**	Test results compared[a] to norm scores or controls**	Questionnaires compared[a] to norm scores of controls**
Kavanaugh et al., 2015 [99]		Behavior: BASC-2 EF in daily life: BRIEF	Elevated symptoms of emotional-behavioral and executive functioning based on parent-rating scales, most prevalent executive functions and behavioral difficulties.		All domains behavior and EF: Epilepsy<norm
Kwon et al., 2012 [92]	General Ability: K-WISC-IV EF: K-FENT WCST Memory: AVLT RCFT Attention: K-ADS SCWT	Behavior: K-CBCL	BECTS appears to be benign at onset but may be at risk for cognitive, behavioral and other psychiatric disorders during the active phase of epilepsy.	All tests: Epilepsy=norm	Behavior: Epilepsy=norm
Lew et al., 2015 [83]	General Ability: WISC-IV short form Social cognition: Strange stories Mind in the eyes	Behavior: CBCL (Social) communication CCC-2	Children with epilepsy have some difficulties in tasks of social understanding. They had poorer structural and pragmatic communication skills.	Mental stories: Epilepsy<controls Physical stories: Epilepsy=controls Other: Epilepsy=controls	Communication: Epilepsy<controls Behavior: Epilepsy<controls

Table 4 continued

Study	Neuropsychological tests*	Questionnaires*	Main outcome**	Test results compared[a] to norm scores or controls**	Questionnaires compared[a] to norm scores of controls**
Modi et al., 2019 [25]		EF: BRIEF Behavior: PedsQL Epilepsy Module BASC-2	Youth with global EF deficits demonstrated lower levels of HRQOL compared with youth without deficits and youth with metacognitive deficits.		EF: Epilepsy<norm Behavior: Epilepsy<norm
Operto et al., 2020 [93]	EF: EpiTrack Junior	Behavior: CBCL	EF impairment in 60% of the sample. Behavior problems in 20% of the sample. At baseline the EpiTrack Junior scores and the CBCL scores are negatively correlated	EF: Epilepsy < norm	Behavior: Epilepsy < norm
Parrish et al., 2007 [84]	EF: D-KEFS	EF in daily life: BRIEF Behavior: CBCL	Impairment in EF was evident for both BRIEF and D-KEFS. Internalizing and externalizing problems were significantly higher.	EF: Epilepsy<controls	EF: Epilepsy<controls Behavior: Epilepsy<controls
Piccinelli et al., 2010 [94]	General Ability: WISC-R/WPPSI Attention: CPT Memory: TEMA EF: WCST	Behavior: CBCL	Attention deficits and behavioral and emotional problems at diagnosis. After treatment specific neuropsychological functions significantly improved. Attention disorders and behavioral problems were more pronounced.	Attention, reaction times after treatment: Epilepsy<norm Other after treatment: Epilepsy=norm	Behavior after treatment: Epilepsy<norm

Table 4 continued

Study	Neuropsychological tests*	Questionnaires*	Main outcome**	Test results compared[a] to norm scores or controls**	Questionnaires compared[a] to norm scores of controls**
Raud et al., 2015 [85]	Sociocognitive: Theory of mind tasks SCQ SSRS Neurocognitive: NEPSY	Behavior: SCQ SSRS	Children with epilepsy encounter several sociocognitive and neurocognitive problems. There is a positive correlation between higher cognitive abilities (executive, verbal and visuospatial) and better ToM.	False belief, intentional lying: Epilepsy < controls EF, attention, language, fine motor skills: Epilepsy < controls Memory, visuospatial: Epilepsy ≤ controls	Social skills: Epilepsy = controls Problem (internalizing) behaviors scale: Epilepsy < controls
Sarco et al., 2011 [100]		EF in daily life: BRIEF Behavior: BASC-2	Correlations between frequency of interictal phenoma and parent-reported problems with mood and externalizing behaviors. Correlations were smaller for behavioral regulation, anxiety, attention and hyperactivity.		Metacognition: Epilepsy<norm Global Executive: Epilepsy=norm Externalizing problems: Epilepsy<norm Other problems: Epilepsy=norm
Schaffer et al., 2015 [86]	General Ability: WISC-IV block design Memory: TOMAL (incl. digit span) RAVLT	Behavior: CBCL TRF	Children with epilepsy have a higher risk for memory and socioemotional problems. Also a higher prevalence of social, internalizing and externalizing problems and distractibility.	All memory except LTM visual: Epilepsy<control	Internalizing, Externalizing, social problems and thought problems: Epilepsy<control

Table 4 continued

Study	Neuropsychological tests*	Questionnaires*	Main outcome**	Test results compared[a] to norm scores or controls**	Questionnaires compared[a] to norm scores of controls**
Schaffer et al., 2015 [86] continued	RCFT Attention: CBCL/TRF attention scale WISC-IV cancelation				
Seidel & Mitchell, 1999 [87]	General Ability: WISC-III Memory: WRAML Mental flexibility: TMT Attention: CPT Language: BNT Motor skills: finger tapping test Grooved Pegboard test	Behavior: CBCL	Some memory difficulties are associated with Carbamazepine treatment. No robust associations between Carbamazepine and cognition or behavior. Improvement in parent rating by retesting.	Memory: Epilepsy<controls Other: Epilepsy (with and without Carbamazepine =controls	Internalizing and externalizing problems: Epilepsy=controls
Stewart et al., 2018 [68]	General Ability: WISC-V EF: Backward digit recall D-KEFS CWIT	(Social) behavior: CBCL (social) SDQ TOMI	There are marked ToM and social impairments, which were not attributable to low intellectual functioning or impaired executive skills. Significantly greater impairment for affective TOM relative to cognitive ToM.	General: Epilepsy<controls EF Epilepsy<controls	(Social) behavior: CBCL: Epilepsy<controls SDQ: Epilepsy<controls TOMI: Epilepsy=controlss

Table 4 continued

Study	Neuropsychological tests*	Questionnaires*	Main outcome**	Test results compared[a] to norm scores or controls**	Questionnaires compared[a] to norm scores of controls**
Stewart et al., 2018 [68] continued	Social cognition Strange Stories task Faux pas			Social cognition: Mental stories: Epilepsy<controls Physical stories: Epilepsy=controls Faux-pas: Epilepsy>controls	(Social) behavior: CBCL: Epilepsy<controls SDQ: Epilepsy<controls TOMI: Epilepsy=controls
Triplett & Asato, 2015 [95]	Neuropsychological: CNSVS (memory, processing and psychomotor speed, EF, reaction time, complex attention and cognitive flexibility)	Behavior: SDQ	Computerized testing in conjunction with parent questionnaires provide an acceptable, time efficient and clinically accessible means to detect early cognitive and behavioral difficulties.	Neurocognition, visual memory, cognitive flexibility, complex attention: Epilepsy < norm Verbal memory, EF, processing speed, reaction time, psychomotor speed: Epilepsy=norm	Emotional symptoms: Epilepsy<norm Other symptoms: Epilepsy=norm
vandenBerg et al., 2018 [96]		EF: BRIEF Behavior: CBCL	There is a (strong) link between executive and behavioral functioning. Subtle differences between parents and teachers ratings suggests different executive function demands in various settings.		EF: Epilepsy<norm Behavior: Epilepsy<norm
Williams et al., 1998 [97]	General Ability: WISC-R/WISC-III Memory: WRAML	Behavior: CBCL Personality: Children's manifest	Cognitive abilities are all in low average range. Only attention skills were reduced and parental ratings indicated attention difficulties.	All: Epilepsy=norm	Attention: Epilepsy<norm Other behavior: Epilepsy=norm

Table 4 continued

Study	Neuropsychological tests*	Questionnaires*	Main outcome**	Test results compared[a] to norm scores or controls**	Questionnaires compared[a] to norm scores of controls**
Williams et al., 1998 [97] continued	Achievement: WJTA Language: PPVT Expressive one-word Picture Vocabulary test Visual motor: Beery Motor skills: Grooved Pegboard EF: WCST TMT CPT	Anxiety Scale-R CDI			Mood, anxiety: Epilepsy=norm

*15-WT=15 Words test, BASC= Behavior Assessment System for Children, BNT=Boston Naming Test, BRIEF= Behavior Rating Inventory of Executive Function, CBCL=Child Behavior Checklist, CCC-2= Children's Communication Checklist, CDI= Children's Depression Inventory, CELF-3= Clinical Evaluation of Language Fundamentals 3rd edition, CNSVS=CNS Vital Signs (computerized neurocognitive test battery), COWA= Controlled Oral Word Association Test, CPT=continuous performance test, CTOPP= Comprehensive Test of Phonological Processing, CVLT= california verbal learning test, CVST= Computerized Visual Searching Task, CWIT: Colour-Word Inference Test, D-KEFS= Delis-Kaplan Executive Function System, FD=freedom from distractibility, GDS= Gordon Diagnostic System Vigilance Task, ITPA= Illinois Test of Psycholinguistic Abilities, KABC= Kaufman Assessment Battery for Children, K-ADS=Kutcher Adolescent Depression Scale, KAIT= Kaufman Brief Intelligence Test, K-BIT= Kaufman Brief Intelligence Test, K-FENT= Korean version of frontal executive neuropsychological test, K-SADS PL= Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime Version, NEPSY= A Developmental Neuropsychological Assessment, PedsQL= Pediatric Quality of Life, PPVT-III= Peabody Picture Vocabular Test 3rd edition, PRS=Parents Rating Scale, PS=performance speed, RAVLT= Rey Auditory Verbal Learning Test, RCFT= Rey complex figure test, RICQ= Readiness for Integrated Care Questionnaire, SCWT= Stroop Color and Word Test, SCQ=Social Communication Questionnaire, SDQ=Strenghts and Difficulties Questionnaire, SSRS=Social Skills Ratings System, TEMA= Test of Early Mathematics Ability, TMT= Trail Making Tests, ToL=Tower of London, TOMAL= Test of Memory and Learning, TOMI: Theory of Mind Inventory, TRF=Teacher Report Form, VMI= Visual-Motor Integration, WASI=Wechsler Abbreviated Scale of Intelligence, WCST=Wisconsin Card Sorting Test, WISC-III=Wechsler Intelligence Scale for Children 3rd edition, WISC-IV/V= Wechsler Intelligence Scale for Children 4th edition/5th edition, WISC-R= Wechsler Intelligence Scale for Children-Revised, WPPSI= Wechsler Preschool and Primary Scale of Intelligence, WRAML= Wide Range Assessment of Memory and Learning, WRAT-3=Wide Range Achievement Test 3rd edition, WJTA= Woodcock-Johnson Tests of Achievement

** AED=anti epileptic drugs, BECTS=benign childhood epilepsy with centrotemporal spikes, BRI=behavioral regulation index, CAE=childhood absence epilepsy, FE=focal epilepsy, FLE=frontal lobe epilepsy, GEA=generalized epilepsy, HRQOL=Health Related Quality of Life, IQ=Intelligence Quotient, LTM=long term memory, RE=rolandic epilepsy, TLE=temporal lobe epilepsy, ToM=Theory of Mind

a '<' = worse, '=' = equals

Which EF deficits can be identified in relation to behavioral functioning?

As was described in the introduction, especially the three subcomponents of cognitive control (working memory, inhibition, mental flexibility) seem to be important EF in relation to behavior. Nevertheless, this part of the review will focus on all aspects of EF.

The relationship between measures of EF and behavioral and/or emotional functioning are shown in table 5. Of the 26 studies, 11 (42%) studies investigated and found an association specifically between an aspect of EF and behavior, which will be discussed in more detail below. Of the studies, 5 were of high quality [68,80,81,85,86] and 6 were of moderate quality [2,25,88,93,94,96]. There were differences in the methodologies and EF instruments. Positively all, but two [2,85] used the CBCL or the BASC-2 to assess several domains of behavioral functioning. This is not very surprising since the CBCL is considered to be a valid instrument for measuring behavioral problems in children with epilepsy [132].

Studies that focussed on global EF reported positive associations between EF deficits and behavioral problems. One study [93] used the EpiTrack Junior, a screening tool for executive functions [133] and reported that the EpiTrack is negatively correlated with the CBCL scores, suggesting that poor EF is related to poor behavioral scores. Unfortunately, statistical data about this association is missing in the study. Another study composed an EF factor with factor analysis out of different tests encompassing sustained attention, problem-solving and visual construction [88]. They found that children who scored lower on this factor were at greater risk for developing internalizing and externalizing behavioral problems. Furthemore, based on children's temperament it appeared that unadaptability (resembling problems in mental flexibility) predicted internalizing behavioral problems, with children with higher scores on unadaptability having higher internalizing problems scores on the CBCL. Resistance to control (resembling inhibition problems) predicted externalizing behavioral problems as well as total behavior problems, meaning that children with some sort of inhibition problems score higher on total behavior problems and externalizing behavioral problems of the CBCL Inhibition as well as mental flexibility problems were suggested to possibly represent early characteristics that put children at risk for relatively longer-term poor behavior outcomes.

Studies using the BRIEF as EF measure [2,25,96] found several associations between BRIEF scores and scores on the behavioral questionnaires. It appeared that having compromised global EF on the BRIEF is related to more internalizing and externalizing behavioral problems, as well as general behavioral symptoms [25]. Especially children with behavioral regulation ('hot' EF including mental flexibility and inhibition) and working memory deficits demonstrated externalizing as well as internalizing behavioral problems [25,96]. Besides working memory, the other more metacognitive aspects of the BRIEF seem to minimally relate to behavior.

A specific association between 'hot' EF and behavior was also reported in several studies using different EF tests. In particular lack of inhibitory control [80,81,88] and behavioral regulation problems [2,82] were associated with behavioral and social problems, confirming the results using the BRIEF as mentioned above. Thus, 'hot' EF problems, especially expressed in behavioral regulation, mental flexibility and inhibition problems, are related to social and emotional behavioral problems as measured by questionnaires as well as test assessment.

Some aspects of 'cool' EF seem also to be related to behavior. This accounts especially for working memory [86] and attention problems [80,81,85,94]. These were associated with social cognitive [80,85,86] and behavioral problems [80,81,85,94]. Hernandez et al. [81] suggest that a part of the behavioral problems in children with FLE is probably attributable to their attention problems, their lack of inhibitory control and their impaired ability to disregard nonrelevant information. Children may also react to constant negative feedback from their social environment, which may result in social problems. Another study [80] suggests specific problems on problem-solving measures whereas particular difficulty was seen with respect to shifting set in response to changing external demands. This was previously described [88] as novelty distress.

These studies seem to confirm that mental flexibility, inhibition and working memory, all the components of cognitive control, are related to several behavioral problems in children with epilepsy. Global EF deficits seem to relate also to behavioral problems.

Besides the abovementioned studies that specifically investigated the association between EF and behavior, 12 studies reported EF and behavior separately, including the three studies with low quality [9,83,84,87,89-92,95,97,98,100]. Of these studies, seven studies [9,83,84,89,90,95,97] showed below-average neuropsychological functioning and above-average scores on behavioral questionnaires, indicating behavioral problems. In these studies the EF domains inhibition [9,83,84], attention [9,89,87,90,95,97] and shifting [83,84,95,97] were below average, whereas in almost all these studies internalizing and externalizing behavioral problems (CBCL) were reported. One study [95], using the SDQ, reported scores within normal range. The proportion of children with abnormal symptom scores was, however, greater than those of the general population in almost all subscales. One study found clinically elevated scores only on the attention problem scale of the CBCL, but average scores on all other problem scales [97]. Thus, although these studies did not examine associations between EF and behavior, it is apparent that the children with EF problems, in particular attention, inhibition and mental flexibility problems, are also reported as having more behavioral problems. This seems to confirm the results of the studies that specifically investigated this association.

Three studies found average scores on cognitive tests as well as reported behavior [87,91,92]. For all of these studies, this might be related to the ecological validity of used tests and/or the lack of availability of adequate EF tests. Two studies [98,100] did not focus solely on cognition, but investigated effects of ASMs on cognition and therefore compared groups [98] or investigated associations with interictal phenomena [100] not presenting data of a normative reference or control group. One study [100] suggests, however, that behavioral regulation problems (as part of EF) in their study might reflect the reported mood problems, which is previously mentioned.

Table 5: Associations between EF and behavior

Study	Epilepsy confounders	Association between EF and behavior
Alfstad et al., 2016 [6]	– Children with early age at onset showed significant higher occurrence of psychiatric comorbidity. – More boys had an ADHD diagnose. – No significant differences with regard to AED use.	EF is associated with psychiatric comorbidity
Ayaz et al., 2013 [9]	– Early age at onset, high seizure frequency and long drug usage are associated with attention. – Epilepsy focus is not associated with attention and behavioral problems.	Not specifically investigated.
Baum et al., 2010 [88]	None.	– Low EF was associated with higher behavior problem scores. – Mental inflexibility predicted internalizing problems. – Inhibition problems predicted externalizing problems as well as total behavior problems.
Bhise et al., 2009 [90]	Children with GEA perform worse on cognition and behavior. Distribution of foci and subtle differences in brain volume appear to be important correlates of cognitive difficulties.	Not specifically investigated.
Braakman et al., 2012 [89]	High seizure frequency is related to poor mental calculation (attention and working memory).	Not specifically investigated.
Burns et al., 2018 [98]	Children prescribed Valproate showed weaker EF compared to children prescribed newer AEDs. Parents of children prescribed Topiramate demonstrated weaker global EF skills and weaker adaptive skills than the children prescribed newer AEDs.	Not specifically investigated.
Conant et al., 2010 [80]	The basal ganglia–thalamocortical circuit might be of influence in the cognitive weaknesses in CAE.	Possible association between attention/behavioral inhibition and social dysfunction.
Giordani et al., 2006 [91]	Children with focal epilepsy performed worse on verbal learning.	Not specifically investigated.
Hernandez et al., 2003 [81]	Younger age relates to more EF problems. Poor seizure control relates to behavior and school problems.	Behavioral and social problems might be related to attention and inhibtion problems
Hessen et al., 2018 [2]	– Early seizure onset was associated with higher and worse scores on both indices of the BRIEF. – No association between AED and EF.	– Behavioral regulation and metacognition correlates high with psychiatric symptoms. – A high level of psychiatric problems contributes to a high level of everyday behavioral executive dysfunction.
Hoie et al., 2008 [9]	None.	Not specifically investigated.

Table 5 continued

Study	Epilepsy confounders	Association between EF and behavior
Kavanaugh et al., 2015 [99]	– Children with epilepsy at younger age show more problems, may decrease in severity with age. – Greater seizure frequency is associated with higher level of EF problems (higher BRIEF BRI)	A family history of psychiatric disorders was associated with internalizing problems and metacognitive aspects of EF.
Kwon et al., 2012 [92]	None.	Not specifically investigated.
Lew et al., 2015 [83]	– Later age at onset was related to more behavioral problems. – Early age at onset was related to lower IQ scores.	There is a relation between social cognition and communication problems for GEA only. There was no significant result for social cognition and behavior.
Modi et al., 2019 [25]	No significant association between EF phenotypes and seizure etiology or epilepsy duration.	– Mood/behavior, EF and impact of epilepsy of the HRQOL seem negatively related to EF impairment – The influence of metacognitive difficulties on HRQOL may be limited to cognitive aspects of HRQOL only
Operto et al., 2020 [93]	No association of EF and behavior with Perampanel.	– Executive functioning was negatively associated with behavior.
Parrish et al., 2007 [84]	None.	There was no association between behavior and tested EF.
Piccinelli et al., 2010 [94]	– Epilepsy is less correlated to cognitive difficulties.	– Children with attention deficit also had behavioral and emotional problems and long reaction times. – Slowness and easy fatigue correlated to anxiety and depression symptoms. – Behavioral problems were correlated with cognitive problems.
Raud et al., 2015 [85]	– Children with early age at onset were overall more impaired. – Longer duration of epilepsy is negatively correlated with attention, visuospatial skills and memory. – Children with GEA and an earlier onset of epilepsy exhibit poorer sociocognitive performance. – Children with GEA have more memory impairment	– Social cognition and social skills seem related to behavior. – False-belief understanding was associated with EF, attention, receptive language and visuospatial skills. – ToM tasks and questionnaires are not related.
Sarco et al., 2011 [100]	– There is a correlation between interictal phenomena and mood and externalizing problems and to lesser extent EF (behavioral regulation). – Spike index highly correlates with depression, aggression and conduct problems. EF is more sensitive to discharges in sleep.	Not specifically investigated.

Table 5 continued

Study	Epilepsy confounders	Association between EF and behavior
Schaffer et al., 2015 [86]	None.	There was a strong relation between social and behavioral problems with memory skills, especially to retrieve information: – Auditory verbal short term memory related to attention, social problems, anxiety and depression – Auditory verbal long term memory related to delinquent behavior and social problems – Impulsive behavior and anxiety in response to memory lapses or school failure
Seidel & Mitchell, 1999 [87]	None.	Not specifically investigated.
Stewart et al., 2018 [68]	Epilepsy severity was associated with social problems. Different AED were related to social cognition.	– Scores on the TOMI were not significantly correlated with scores on behavioral measures of ToM – There was a significant correlation between ToM and social competence in children and adolescents with GGE
Triplett & Asato, 2015 [95]	None.	Not specifically investigated.
vandenBerg et al., 2018 [96]	Longer duration of epilepsy and early age at onset were related to mood problems.	– There was a high correlation between behavioral regulation and internalizing and externalizing problem behavior. – Attentional and social behavior problems correlated high with working memory.
Williams et al., 1998 [97]	No hemispheric-specific effects.	Not specifically investigated.

Note. ADHD=attention deficit hyperactive disorder, AED=anti epileptic drugs, BRIEF BRI= Behavior Rating Inventory of Executive Function Behavioral Regulation Index, CAE= childhood absence epilepsy, EF=executive function, FLE=frontal lobe epilepsy, GEA=generalized epilepsy, IQ=intelligence quotient, SDQ= Strenghts and Difficulties Questionnaire, ToM=Theory of Mind

Which social cognition problems can be identified in relation to EF and behavioral functioning?

As stated above, social functioning problems may occur when social cognition difficulties are present. There is little evidence thus far linking social cognition problems and EF deficits in children with epilepsy. We want to explore this relation more specifically. We found three studies that investigated this association [68,83,85]. Stewart et al. [68] used working memory and inhibition as covariates because the children with GEA in their group performed lower compared to the control group on these domains. The evident ToM and social impairment in the children in this study were not attributable to the impaired working memory and attention skills (specifically inhibition) while this association is often mentioned in typically developing children [134]. It appeared that especially higher affective ToM was correlated with higher social behavior and less social problems. This could not be found to the same extent with cognitive ToM. In this study, parent report did not show impaired social skills, which were suggested to be related to the differences in skills measured by these instruments (basic social cognitive skills and earlier emerging cognitive ToM in the questionnaire vs higher social cognitive skills and higher affective ToM in test assessment). Raud et al. [85] did found a positive correlation between EF and ToM false belief measures, which infers that children who have a EF deficit have a poorer understanding of other's mental states. They also found that children with better social skills, tested as well as reported, also tended to have better social cognition. Children with better social cognition tended to have less behavioral problems. Lastly, they suggest that the development of ToM in children with (early onset) epilepsy shows delayed progress despite normal IQ, but that the development follows the same developmental pattern as typically developing children. This might imply that children could catch up in the long term. One study [83] reported no association between social cognition and behavior.

The association of EF and social cognition and social behavior in children with epilepsy is under-researched and therefore underreported in this review. The few studies seem, however, to confirm that there is a relationship, as the results of studies in children without seizures seem to suggest. This scarcity of studies on this calls for future research.

Can EF deficits be associated with psychiatric comorbidity?

Most studies investigating EF excluded children with psychiatric diagnoses, which possibly obscures these data. Two studies reported a link between EF and psychiatric comorbidity [2,6]. It appeared that children with high scores on EF tests as well as the BRIEF indices were reported as having worse scores on a questionnaire for psychiatric symptoms. A high level of psychiatric problems in boys contributed to a high level of everyday behavioral executive dysfunction [2]. Alfstad et al. [6] found that EF deficits are an independent risk factor for psychiatric comorbidity, but points out that impairment in EF also occurs in various neuropsychiatric disorders in children in the general population, and that the deficit could be considered an integral part of the psychiatric disorder. One study found an association between a family history of psychiatric disorders and the main indices of BRIEF and the BASC [99]. It suggests that those children with epilepsy with a family psychiatric history are at the greatest risk in developing EF as well as behavioral problems.

Early problematic behaviors might be identified as predictors for the development of psychiatric problems [88] or even suits a psychiatric diagnose [6], but the lack of data of children with psychiatric diagnoses makes it challenging to comment whether a direct link between EF and psychiatric symptoms is present in children with epilepsy.

Potential confounders

Certain factors may have biased results of the reviewed studies, thus playing a moderating role in the relationship between EF and behavior. All studies that reported about possible relationships, corrected for such potential confounders (age, gender, IQ) and still found correlations between measures of EF and behavior. For example, most studies that statistically corrected for age-effects showed that this in general could not account for the found significant relationship. Four studies [2,93,99,100] reported that younger age was associated with worse behavioral scores. Furthermore, younger age was mentioned in two studies [2,81] as being negatively associated with EF. In these studies, children with younger age at examination achieve lower results on EF compared to older children. It could be hypothesized that this association is mediated by early age at onset, as early disruption of the young brain might lead later on to more problems (the well-known 'growing into deficit'). This was controlled for in nine studies, while five studies [2,6,9,85,96] confirmed that early age at seizure onset was associated with lower EF scores. This may lead to the conclusion that not young age, but rather younger age at seizure onset puts a child with epilepsy more at risk in developing EF problems.

Level of intelligence or education level, which is another important confounder, was corrected for in all studies by including only participants with IQ within normal range. Only in one study [83] IQ was negatively associated with social cognition.

In the literature, gender is normally seen as a potential confounder. In the included studies there was equal distribution of boy/girl in the studies. Gender appeared not to be of significant influence in the relationship between EF and behavior. Only one study [6] reports that male gender is associated with psychiatric comorbidity. Furthermore, boys seem to be more at risk in developing more externalizing behavioral problems compared to girls [2,85].

When associating epilepsy with behavioral problems, EF was identified as a potential mediator in four studies [2,6,68,88]. Impairment in EF occurs in various neuropsychiatric disorders in children in the general population, and the deficit could be considered an integral part of the psychiatric disorder or behavioral issues [6,88]. It has been argued that EF dysfunction could cause increasing difficulties with age on several domains as children are expected to develop independence and learn to demonstrate e.g. appropriate social behavior. Working memory as well as inhibition are seen as important covariates when assessing for social cognition and social problems [68].

In summary, the relationship between EF and behavior seems unlikely to be largely explained by factors such level of intelligence and gender. Age might be an important factor, possibly linked to early age at seizure onset. More research is needed especially on the potential mediating role of EF (excluding IQ) when investigating epilepsy and behavior.

Discussion

The aim of this review was to explore the association between EF and socioemotional problems in in children with epilepsy. Increasing knowledge on this matter could contribute to development of specific intervention programs for children with epilepsy and their caregivers. The review showed that the associations between executive functions and behavioral and socioemotional problems are under-researched in children with epilepsy with just 26 studies identified, being very heterogeneous as far as materials and participants are concerned. The subject is also relatively new with more than 80% (21) of the studies conducted in the past 10 years, with mostly moderate quality. Overall, the findings suggest that (at least) below average EF performance is related to above-average behavioral problems. Given the large procedural differences of these studies and the relatively small number of studies with good quality, it appeared difficult to make detailed comparisons and generalizations. Despite these shortcomings, the results of the present review did reveal some interesting aspects, which will be discussed in more details below.

The majority of studies reported no significant difference in EF scores of children with epilepsy compared with controls without epilepsy or a normative sample. This was true when cutoff values of the manual were used. The proportion of children with epilepsy with below-average scores (but within cutoff limits), however, was greater than those of the general population. It is common for clinical used tests, not to detect the problems patients encounter in daily life functioning, which is often related to ecological validity of the traditional tests [chaytor]. Most objective (neuropsychological) tasks rely upon explicit mechanisms for understanding the task and for providing the response (each one having a single, intrinsic correct solution), while most of our actions in daily life are automatic or have little access to conscious monitoring [135]. (Subtle) cognitive differences, which are mostly expressed only in unstructured environments as at home [136], are therefore hard to capture in a structured clinical test setting. Despite this, in this review there's still a large group with some difficulties in EF on test assessment. With regard to the association between EF and behavior it is worth mentioning that in general a direct relationship between performance-based measures and proxy (behavioral) measures is not consistently found. We chose also to include studies that used the BRIEF as measurement of EF, as this reflects more daily "real-life" behavior. Different measures can contribute in a different way to the assessment of EF [137]. Importantly, also BRIEF scores in many clinical populations, rarely correlate with cognitive tests [15,138]. The BRIEF is considered a valid instrument for people with epilepsy [139]. Additionally, correlations between the BRIEF and the CBCL (the behavioral questionnaire most frequently used) are high [96]. EF difficulties in this review were confirmed by the parent proxy reports with the BRIEF. This implies that children with epilepsy encounter EF problems in different settings. Parents, however, reported far more EF problems than suggested by test assessment. This seems to be explained by the different EF demands across settings as well as the difference in measurement as stated above. Another way to identify specific EF deficits is the use self-report questionnaires. All studies included in this review failed to use self-report questionnaires so self-reports about EF are missing. This is largely due to the participants' young age and therefore limited reading skills and limited self-awareness, which makes the use of self-report questionnaires not possible.

The aforementioned difficulties in EF experienced by children with epilepsy span a wide range of abilities and thus may suggest impairment across a wide range of aspects of EF. Attention deficits as well as working memory problems are the most marked cognitive problems. Both are frequently reported in patients with epilepsy and will be discussed in more detail below. In general it seems that global EF deficits, instead of an isolated EF deficit, gives the highest risk factor for poor psychosocial functioning across behavioral and emotional domains [25]. At this time, the wide range of assessment instruments used and the diversity in samples, mainly of epilepsy types, makes it difficult to comment on whether or not particular aspects of EF are more likely to be affected. Early age at seizure onset as well as high seizure frequency seem to be mostly related to impaired EF. This review, however, focuses on studies that investigated associations between EF and behavior. A great amount of studies investigating only EF were therefore not included.

In contrast to the EF problems, behavioral problems were, as suspected, reported in 77% of the studies. This included a wide range of behaviors measured with a variety of tests. Although the Achenbach scales were used in 16 studies, which represent a strength in this review, the different scales and subscales unfortunately still make it difficult to identify a specific problematic behavior. "Attentional problems" was the most reported problematic behavior on the behavioral questionnaires. This is not surprising; as discussed in the introduction, the rate of comorbid ADHD in epilepsy is high [62] and attentional problems can be directly related to different epilepsy variables [45]. Importantly, the subscale "attention problems" of the Achenbach scale asks not only about different sorts of attention,

but also includes questions about cognitive control (e.g. inhibition and flexibility) [19,140,141], a main finding in this review. It could be hypothesized that a high rate on this scale not only reflects attentional problems, but also reflects global EF deficits in children with epilepsy. From a clinical perspective, item inspection of subscales when interpreting the results is recommended. Unfortunately, the data of all items were not available for this review. Some studies reported only about general internalizing and externalizing problems, without even reporting about the underlying subscales. Surprisingly, there were also six studies that reported no behavioral problems. It has been suggested that (neuro)behavioral problems in children with epilepsy are underestimated due to, for example, excluding children with low IQ [88] or to under-identification of neurobehavioral comorbidities [99]. Parents' low expectations with their child's academic performance and life achievement [81] may uplift questionnaires' scores, as they rate children doing quite well despite the circumstances.
With regard to the main focus of this review it appeared that only 14 of the 26 included studies specifically studied the association between EF and psychiatric and socioemotional behavioral problems. The remaining studies reported about cognitive and behavioral problems separately. In the majority of these studies, shifting and inhibition (used in different terms in different studies), regularly seen as 'hot' EF and both part of cognitive control, were especially related to externalizing behavioral problems. Problems in these two areas cause an inability to adequately adjust behavior as well as an inability to lower the interference of unwanted stimuli or responses. Moving between multiple tasks is also disturbed. As far metacognitive 'cool' EF problems concerns, it seemed that especially working memory (also being part of cognitive control) and attention are most related to behavioral problems. These two are two well-defined cognitive constructs, in which there is compelling evidence linking both constructs to each other [49]. From a daily life perspective, poor working memory capacity impacts in many different situations by constantly forgetting information. Attention on its own, has been extensively studied in different patient groups including epilepsy, while a direct link between attention and behavior is already established many times [e.g. 142]. These problems in cognitive control lead to, among others, poor sustained attention, weak attentional switching and impulsive behavior [141,143]. It makes perfectly sense that a deficit in these areas leads irrevocably to social and emotional behavioral problems. From a daily life perspective, it's already quite a challenge for a typically developing child to constantly adjust to the environment, ignore a proliferation of stimuli and remember important information. In the case of a child with epilepsy, this challenge even becomes larger as epilepsy on its own impacts in many different direct and indirect ways. As was mentioned earlier, early age at onset is a variable that needs to be considered in the development of EF problems. Especially since independent of neurological problems, there is evidence that behavioral disinhibition in early childhood may be linked with

later disruptive behavior and comorbid mood disorders in normally developing children [144]. Furthermore, high seizure frequency is an important factor in the relationship between EF and behavior. Importantly however, studies have also shown that children with adequate seizure control still can exhibit EF and behavioral problems. This implies that seizures are not solely the cause of these difficulties, but might co-exist with EF deficits as a symptom of the underlying epileptogenic condition [70]. Surprisingly, the localization of the epilepsy does not seem to contribute as much as expected. As was described in the introduction, the frontal lobe plays a major role in EF development and a specific relationship between EF and behavioral problems might be expected in children with FLE. The findings for this were inconsistent, but the one study that did find a difference based on seizure localization in focal-onset epilepsy was consistent with FLE having more EF problems. Additionally, in other studies, also duration of epilepsy is often mentioned as an important epilepsy variable. With only two studies reporting about this variable, we cannot confirm this in the current review.

Overall, this review seems to confirm that there is an association between EF deficits and behavioral problems in children with epilepsy. Specifically the three subcomponents of cognitive control (shift, inhibit and working memory) are linked to especially externalizing behavioral problems. Although we were able to cautiously identify two important epilepsy variables, the exact impact of epilepsy variables on this relationship remains to be an important subject for further investigation.

Another interesting finding was the association between EF and social cognitive behavior. This might be expected [69] as recent studies [145,146] suggest that social cognition is impaired in temporal lobe epilepsy (TLE) and a part of the sample in our review had temporal lobe epilepsy or temporal epileptiform activity on EEG recording. The review suggests that impairments in EF might underlie or account for impairments in some aspects of social cognition in children with epilepsy. This concurs with studies in typically developing children [e.g. 147]. Interestingly in these studies, cognitive flexibility, inhibition [147] and working memory [148] were named as important EF associated with social cognitive aspects [147]. So again, cognitive control seems to impact an important aspect of daily life functioning: social functioning.

Only two studies in this review investigated the relationship between EF and psychiatric diagnoses in children with epilepsy, while this relationship is confirmed in other patient groups [149,150]. These two studies seem to suggest that EF problems are associated with psychiatric comorbidities. Unfortunately, psychiatric diagnoses are often an exclusion criteria in most of the studies. Nevertheless, there might be some cognitive as well as behavioral problems that can be seen as precursors for psychiatric disorders. Cognitive flexibility for instance was suggested in one study to be a marker for anxiety problems [88]. Several EF deficits we found in the studies are also frequently seen in children with autism spectrum disorder and ADHD [150,151]. It is important to note the possible bidirectional relationship between executive dysfunction and psychiatric disorders; having a psychiatric disorder could also be a predictor of executive difficulties [6]. For future studies it is essential to also include children with epilepsy and different comorbid psychiatric diagnoses in order to discriminate more accurately between different groups

Lastly, we identified age as possible confounder that could moderate the found associations. This might be related to early age at seizure onset. The more demographic factors such as level of intelligence and gender seemed hardly of any influence.

Limitations and recommendations of this review

This review was conducted in accordance with PRISMA guidelines, but there are limitations. Only including English language articles may have resulted in publication bias. Limiting literature searches to peer-reviewed publications may have reduced the number of studies included in this review; this approach, however, probably enhanced the likelihood that studies included in this review were of good quality. Additionally, we rated the quality of the studies with the NOS. This kind of 'quality score' approach might have reduced scientific judgment [152]. The inter-rater reliability between individual reviewers using the NOS was poor on some items [153,154]. We also did not contact authors for missing information, which could have obscured some of the data [154]. Unfortunately, due to the limited number of studies and the heterogeneity of tests used to assess executive functioning and behavior, it was not possible to undertake meta-analyses, which would provide more precise information.

There is also a lack of population-based data, due to missing control groups. The majority of participants were recruited from hospital-based samples, which limits the generalizability of results to all children with epilepsy. Another limitation is the definition of (aspects of) EF as well as behavior. To assess EF, a wide range of tests, inventories, and tasks have been developed in countries with different cultures, developmental levels, and different languages, and also normed in unlike settings [155]. It is not surprising that different studies often do not find (similar) associations between medical and psychological conditions. An essential problem in neuropsychological evaluation is the lack of uniformity concerning labeling of performance test scores [24]. We need to recognize: the lack of reliability in applying test descriptors; inconsistency of test publishers in their recommendations for descriptors of the scores of their test; identification of an 'impaired' test score range and 'test bound', meaning that one considers each specific test score as having inherent clinical meaning, without considering the overall test result profile and the particular examinee's life context. From this perspective it makes it more difficult to comment on whether a specific test score in the studies is deviant or not.

Future research should take into account well-defined conceptualizations of

EF and behavior. Distinguishing specific aspects of EF may shed more light on the association between specific EF and behavior in children with epilepsy. It is also important to realize that EFs are expressed differently in young and older children. Some EFs might be seen as predictors for disruptive behaviors when growing up [88] and increase the risk of internalizing and externalizing behavior problems [85,88]. Early intervention is therefore highly recommended. Combining neuropsychological evaluation and intelligence testing with parent proxy reports, and when applicable self-report, were suggested as acceptable ways to detect (early) cognitive and behavioral difficulties [84,95,97] and may help to identify strengths and weaknesses to start appropriate intervention.

Conclusion

Children with epilepsy exhibit different EF deficits, while attention deficits and working memory problems seem common. Parents report a variety of internalizing as well as externalizing behavioral problems. Three aspects of cognitive control (working memory, shift, inhibit) and attention deficits seem mostly associated with especially externalizing behavioral problems in children with epilepsy. It is suggested that these cognitive control deficits might also be related to social functioning. Specifically the epilepsy variables early age at seizure onset and high seizure frequency are important (possible causal) variables in the relationship between EF and behavior. For future studies, defining specific aspects of EF and behavior is required. More studies into the association between EF and behavior are needed to gain insight into the strengths and weaknesses to develop appropriate and early intervention.

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Appendix A: search terms

Theme	Term
Executive function	Executive function Executive dysfunction Frontal Attention/concentration/attentional Cognitive flexibility/Shift Cognitive inflexibility Inhibition Impulsivity/impulsiveness Working memory Social cognition Empathy Emotion recognition Mental control Self regulation Planning Organization Problem-solving Cognitive control
Epilepsy	Epilepsy Epileptic Seizure Attack
Behavior	Behav* Emotion* Social* Psych*
Child	Child* Pediatr* Young* Schoolage Youth Adolescen*

CHAPTER 3

Executive and behavioral functioning in pediatric frontal lobe epilepsy

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Abstract

Objective: Epilepsy, as a chronic and neurological disease, is generally associated with an increased risk for social and emotional behavior problems in children. These findings are mostly derived from studies on children with different epilepsy types. However, there is limited information about the associations between frontal lobe epilepsy (FLE) and cognitive and behavioral problems. The aim of this study was to examine relationships between FLE and executive and behavioral functioning reported by parents and teachers.
Material and methods: Teachers and parents of 32 children (18 boys, 14 girls, mean age 9; 2 years ±1;6) with a confirmed diagnosis of FLE completed the Behavioral Rating Inventory of Executive Function (BRIEF), the Child Behavior Checklist (CBCL), and Teacher Report Form (TRF). Results: About 25 to 35% of the parents and teachers rated children in the abnormal range of themain scales of the BRIEF, CBCL, and TRF. Teachers tend to report more metacognition problems, whereas parents tend to report more behavior regulation problems. Children with left-sided FLE showed more problems than children with bilateral or right-sided FLE. The whole range of executive dysfunctioning is linked to behavioral dysfunctioning in FLE, but ratings vary across settings and informants. The epilepsy variables age of onset, lateralization, drug load, and duration of epilepsy had only a small and scattered contribution. Conclusion: Ratings on the BRIEF, CBCL, and TRF are moderately to highly correlated, suggesting a (strong) link between executive and behavioral functioning. Subtle differences between parents and teachers ratings suggest different executive function demands in various settings.

Introduction

Epilepsy is the most common neurological condition in childhood with a prevalence of 4-10 per 1000 [1]. Research on psychiatric comorbidity is extensive and it is well-recognized that epilepsy as a chronic and neurological disease is associated with an increased risk (up to 60%) of social and emotional behavior problems in children [2,3]. Common comorbidities include attention-deficit/hyperactivity disorder (ADHD), autism, anxiety problems and depression [4-9]. These problems are often present around the time of diagnosis, diminish over time [10], and appear to be associated with neurologic dysfunction, severe seizures [2] and family dysfunction [11].

Most studies have focused on temporal lobe epilepsy (TLE) because it is the most frequent type of epilepsy [12,13]. We question the generalizability of findings to other types of epilepsy, in particular frontal lobe epilepsy (FLE). TLE and FLE differ with respect to localization and functionality. To date, there is evidence for association between FLE and attention and inhibition problems, social cognitive problems and aggression [13-18]. Executive functions (EF) are mainly localized in the frontal lobe and is an 'umbrella' term for the management (regulation, control) of cognitive processes like attention, inhibition, initiation of activity, working memory, mental flexibility, planning and organization and problem solving strategies [19]. It consists of the capacities that enable a person to engage successfully in independent, purposive, self-directed and self-serving behavior [20]. There is growing evidence of neuroimaging studies that frontal lobe epilepsy leads to structural and functional disorders [12,13]. Also, seizures as well as interictal epileptic discharges are increasingly recognized to interfere with physiological brain circuitry [12], which in the long term can result in chronic cognitive and behavioral comorbidity [12,13,21]. Frontal lobe epilepsy could therefore lead to executive function problems, which can be expressed in behavioral problems and social and academic failure [13,21-26]. Furthermore, TLE and FLE differ with respect to seizure characteristics. In FLE nocturnal seizures are far more frequent than in TLE and therefore poor quality of sleep is common. This factor on its own may be associated with a variety of behavioral and cognitive problems [27-29].

It is therefore worthwhile exploring executive and behavioral functioning and their interaction in pediatric FLE. Since clinically used performance-based measures do not always have good sensitivity and specificity, the use of parent and/or teacher-proxy measures is generally accepted for measuring emotional and behavioral problems. The Behavioral Rating Inventory for Executive Function (BRIEF) has rarely been used in studies on children with epilepsy, however a few authors mention inclusion of FLE [30-32], usually reporting frequent executive dysfunction. Reports from parents as well as teachers are complementary for the BRIEF [33], but have only been studied in one study [30]. The CBCL and TRF are questionnaires which are used extensively in pediatric epilepsy, showing elevated scores [34,35] and are considered to be a valid instruments for measuring behavioral problems in children with epilepsy [36]. This has been sparsely studied in children with FLE [36-38]. Finally, the influence of epileptic lateralization, age of onset, duration of epilepsy and drug load are evaluated.

Material & Methods

Participants

Children with FLE were referred by the neurologist for a broad neuropsychological assessment. The assessment of executive functioning with validated and normative tests is possible from the age of eight. Further executive function demands differ in primary and secondary school and in the Netherlands children go to secondary school at approximately the age of twelve. Also, longer duration of epilepsy is considered a risk factor for developing psychopathology. Therefore inclusion criteria were age between 8 and 12 with a diagnose frontal lobe epilepsy and IQ > 70 or school achievement scores above C level (Dutch CITO) in math and language. Exclusion criteria were health and/or psychiatric problems, which could influence the neuropsychological assessment, except for attention deficit and hyperactivity disorder (ADHD), which is very common diagnosed in children with epilepsy [41]. A total of 32 children (18 boys, 14 girls) met these criteria, 5 of these children had a confirmed ADHD diagnosis. For the BRIEF, 32 parents and 30 teachers completed the questionnaire. For the CBCL and TRF 31 parents and teachers completed the questionnaire. The definition of the type of epilepsy was based on the International League Against Epilepsy criteria and confirmed by an EEG registration.

Study procedures

The children who met the inclusion criteria were invited for neuropsychological assessment in the psychology department of our tertiary epilepsy centre. Questionnaires were completed by the parents of the children while children were assessed with performance-based measures. When a parent did complete the questionnaire and a teacher did not or vice versa, we still used the completed form in our data. Questionnaires for the teachers were delivered by the parents or sent by mail. The study was approved by the Ethical Committee of MST Enschede and parents gave their informed consent.

Measurements

Executive functioning in this study was measured using the Behavioral Rating Inventory for Executive Function (BRIEF) [42,43]. This questionnaire is an 86-item questionnaire designed to assess executive function in daily life in children ages 5 through 18 years and is a valid instrument for people with epilepsy [44]. It includes a parent and a teacher form to assess both home and school environments.

Each form contains 86 items in eight non-overlapping clinical scales and two validity scales. These theoretically and statistically derived scales, form two indexes, both consisting of subscales:

a. Behavioral Regulation Index (BRI): Inhibit, Shift and Emotional Control;
b. Metacognition Index (MC): Initiate, Working Memory, Plan/Organize, Organization of Materials and Monitor.

All scores form the Global Executive Composite (GEC) which takes into account all of the clinical scales and represents the child's overall executive function.

According to the manual of the BRIEF a, a score 1.5 SD (≥ percentile 93) above average was considered statistically significant for the BRIEF and indicates executive function problems.

The social and emotional behavior of children was assessed using the Child Behavior Checklist (CBCL) and teacher report form (TRF) [45,46]. It contains descriptions of 118 behavioral and emotional problems. The respondent is asked to rate the child's behavior over the previous 6 months on a graded scale (0-2). The resulting profile consists of a total problemscale and two main scales which consists of eight subordinate problem scales:

a. Internalizing Problems with the subordinate scales: Anxious/depressed, Depressed, Somatic complaints, Social problems, Thought problems and Attention problems.
b. Externalizing Problems with the subordinate scales: Delinquent Behavior, Aggression.

For the CBCL and TRF, according to the manual, a score 1.33 SD (≥ percentile 90) above average was considered statistically significant for the main scales and indicates behavioral problems. For the underlying problem scales this is 2 SD (>= percentile 97).

The CBCL/TRF as well as the BRIEF are validated for the Dutch commercial market [43,46] and are therefore translated into Dutch. In addition, there is a Dutch normative reference sample.

Statistical analysis

Data, corrected for age, were compared with normative data of the Dutch population. Intraclass correlation (ρ) analyses were carried out to explore the consensus of the two informants (parent and teacher) on the BRIEF and the CBCL and TRF for normally distributed variables. Spearman correlations were calculated when data were not normally distributed.

Younger age of onset as well as longer duration of epilepsy are described as risk factors for developing cognitive [47,48] and behavioral disorders [49-51]. To explore the effect of epilepsy related factors on the scores of the questionnaires, we therefore categorized participants into different groups: age at seizure onset (young < 5 years vs old ≥ 5 years), duration of FLE (short < 5 years vs long ≥ 5 years) and additional left vs right vs bifrontal lateralization (based on EEG), and drug load (none, monotherapy, polytherapy). ANOVA and, when results were significant, independent t-tests and nonparametric tests in case of small numbers in subgroups at the 5% significance level were used to compare the groups on continuous variables. Multivariate regression analyses (enter) were carried out with the epilepsy variables as the independent variables and the results of the questionnaires as the dependent variables. Data were analysed using the Statistical Package for Social Sciences (IBM SPSS Statistics 20.0).

Results

The demographic characteristics and epilepsy variables of 32 children are presented in table 1.

Table 1: Demographic and epilepsy variables

Characteristics	Value
N	32
Patients	
1. Gender (male:female)	18:14
2. Mean age (±SD) in years at assessment	9.2 ±1.6
Age at seizure onset	
3. Mean age (±SD) in years	4.6 ± 2.8
4. Young age (< 5 years)	16 (50%)
Duration of epilepsy	
1. Mean duration (±SD) in years	4.6 ± 2.7
2. Short duration (< 5 years)	17 (53%)
3.	
Seizure focus based on EEG	
1. Left frontal	11 (34%)
2. Right frontal	6 (19%)
3. Bifrontal	11 (34%)
4. Unknown lateralisation	4 (13%)
AED treatment	
5. Monotherapy	12 (38%)
6. Polytherapy	16 (50%)
7. No AED	4 (12%)

BRIEF

Figure 1a and 1b show that about 25 percent of the children were rated in the abnormal range on the Global Executive Composite (GEC) and the two indices (Behavioral Regulation index (BRI) and Metacognition index (MC)) of the BRIEF. With respect to the eight subscales it appeared that teacher scores were, on average, higher than parents' scores. The correlations (all $p < 0.05$, except for 'initiate') of the teachers' and parents' BRIEF scores for the normally distributed subscales 'working memory', 'plan/organize', 'emotional control' and the index 'metacognition' ranged from $\rho = .4$ to .7. The correlations for the remaining, not normally distributed subscales, index and the GEC ranged from $r_s = .5$ to .7.

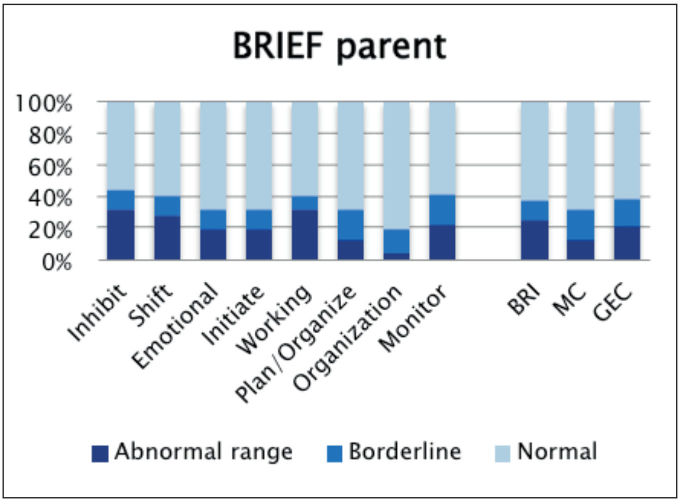

Figure 1a: Scores BRIEF parent

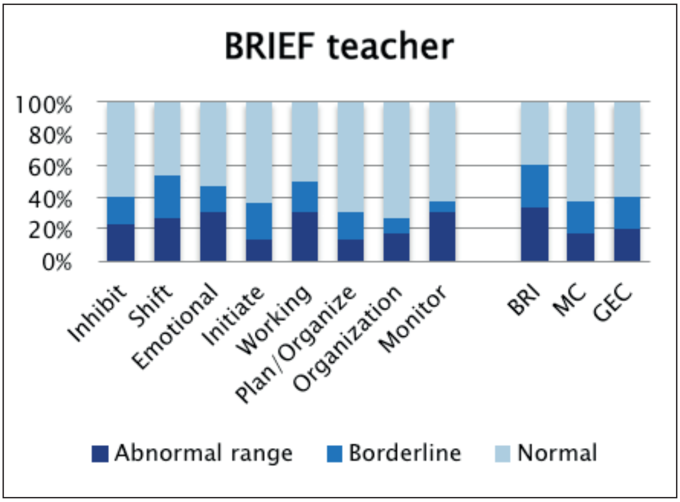

Figure 1b: Scores BRIEF teacher

Influence of epilepsy variables on the BRIEF scores
There were no significant differences in the BRIEF scores among children with the different epilepsy variables (including gender) on the parents' scores. For teachers' scores children with left-sided lateralization had higher ratings than those with bifrontal lateralization on the subscales 'emotional control' (p =. 03, CI [.74, 9.64]) and 'inhibition' (U = 22.50, p = .02). The subscale 'initiate' (p = .03, CI [-5.9, -.37]) was rated lower in children taking monotherapy than children taking polytherapy. Overall, regression analyses showed that none of the epilepsy variables (including gender) were related to the scales of the BRIEF for both parents and teachers.

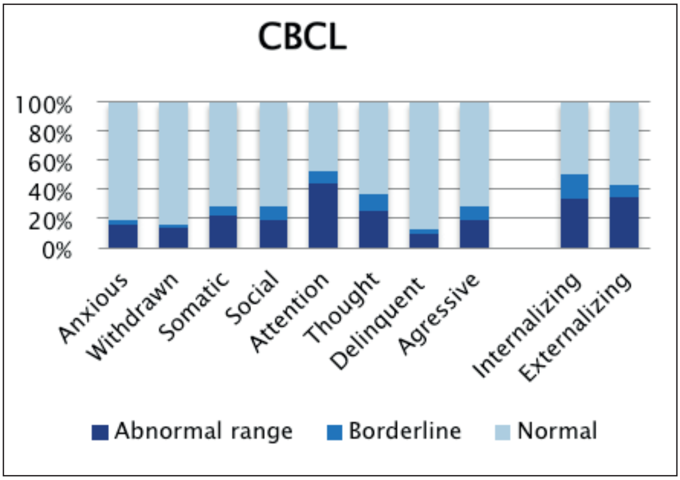

Figure 2a: CBCL scores

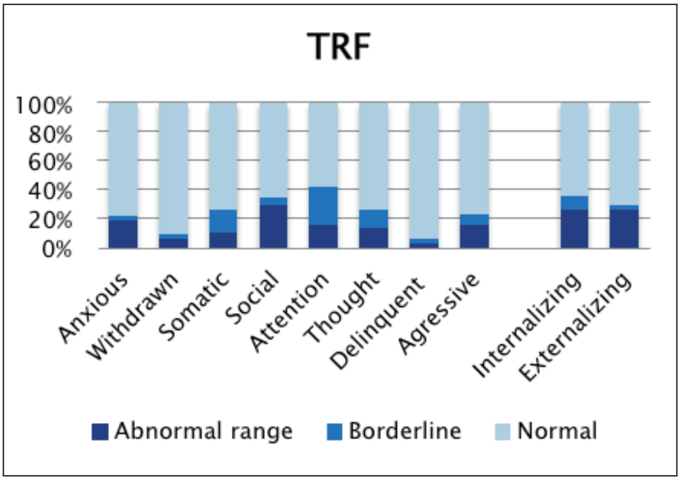

Figure 2b: TRF scores

CBCL and TRF

Figure 2a and 2b suggest that about 35 percent of the children were rated in the abnormal range on the two Problem Scales by parents. For teachers this was 25 percent. As indicated by figures 3 and 4, respectively 44% and 16% of the children were rated in the abnormal range of the attention problem scale by respectively parents and teachers.

Significant correlations ($p < 0.05$) were found between nearly all parents' and teachers' subscales and Problem scales (Internalizing and Externalizing) and ranged from $r_s = .4$ to .7. Only correlations for the problem scales 'thought problems' and 'somatic problems' were not significant.

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Influence of epilepsy variables on CBCL and TRF

For the CBCL, comparison between groups revealed no significant different influences by age of onset, duration of epilepsy and drug load on all domains. Boys ranked higher on 'thought problems' ($U = 75.00$, $p = .05$) and 'rule-breaking behavior' ($U = 75.00$, $p = .05$). Children with left FLE were rated higher on 'externalizing' ($U = 26.50$, $p = .02$), 'aggressive' ($U = 25.50$, $p = .02$), 'rule-breaking' ($U = 26.00$, $p = .02$) and 'social' ($U = 24.50$, $p = .02$) behavior problems compared to bifrontal focus. Compared to right FLE, children with left LFE ranked higher on 'thought problems' ($U = 12.00$, $p = .04$). Overall, regression analyses showed that only duration of epilepsy ($ß = .22$) and age of onset ($ß = .22$) contributed to the variance of the subscale 'withdrawn/depressed') ($F(31) = 3.81$, $p = .03$)

For all domains of the TRF there were no significant differences between any of the groups. Only children with left FLE were ranked higher than those with bifrontal FLE on 'aggressive behavior' ($U = 25.50$, $p = .05$). Regression analyses showed that thirteen percent of the variance of the subscale 'anxious/depressed' of the TRF was explained by the epilepsy variable lateralization ($F(30) = 4.16$, $p = .05$, $ß = -.35$).

Executive vs behavioral functioning

Table 2 shows the correlations between the ratings for the BRIEF parent and the CBCL. Most of the correlations between the BRI and its underlying subscales and the domains of the CBCL were significant and of high magnitude. Few of the subscales of the MC correlate with the domains of the CBCL. Only the domain attention problems of the CBCL show high correlation with the MC, and is especially high with the subscale working memory ($r_s = .80$, $p < .0001$).

The correlations for the BRIEF teacher and the TRF are shown in table 3. The MC is significantly correlated with all domains of the TRF, with attention problems and aggressive behavior showing the highest correlations (respectively $r_s = .83$, $p < .0001$ and $r_s = .70$, $p < .0001$). The main Problem Scale 'externalizing problems' of the TRF shows strong correlations with the global executive composite (GEC) and all underlying subscales, except for 'initiate'.

Table 2: Spearman correlation analyses between CBCL and BRIEF

TRF \ BRIEF	Inhibit	Shift	EC[1]	Initiate	WM[2]	Plan[3]	OM[4]	Monitor	BRI[5]	MC[6]	GEC[7]
anxious/depressed	,480**	,727**	,635**	,636**	,429*	,553**	0,25	,495**	,494**	,452*	,433*
withdrawn/depressed	0,229	,470**	,424*	,472**	0,321	,391*	0,232	0,31	0,228	,376*	0,22
somatic complaints	,496**	,486**	,461*	0,361	,368*	,498**	0,177	,419*	0,316	,397*	0,291
social problems	,519**	,670**	,626**	,662**	,536**	,606**	,441*	,609**	,466**	,557**	,455*
thought problems	,381*	,392*	0,329	,434*	,511**	,567**	0,293	,409*	0,258	,493**	0,327
attention problems	,854**	,711**	,661**	,707**	,821**	,870**	,626**	,873**	,593**	,834**	,724**
rule-breaking behavior	,563**	,567**	,580**	0,204	0,311	,424*	,463**	,486**	,384*	,530**	,362*
agressive behavior	,901**	,698**	,753**	,386*	,573**	,633**	,554**	,818**	,626**	,704**	,613**
internalizing	,405*	,658**	,581**	,602**	,449*	,527**	0,304	,471**	,427*	,425*	,418*
externalizing	,743**	,586**	,634**	0,344	,536**	,570**	,640**	,742**	,490**	,673**	,549**

* Correlation is significant at the 0.05 level, ** Correlation is significant at the 0.01 level,1 Emotional Control, 2 Working memory, 3 Plan/Organize, 4 Organization of Materials, 5 Behavior Regulation Index, 6 Metacognition index, 7 Global Executive Composite

Table 3: Spearman correlation analyses between TRF and BRIEF

BRIEF / TRF	Inhibit	Shift	EC[1]	Initiate	WM[2]	Plan[3]	OM[4]	Monitor	BRI[5]	MC[6]	GEC[7]
anxious/depressed	,480**	,727**	,635**	,636**	,429*	,553**	0,25	,495**	,494**	,452*	,433*
withdrawn/depressed	0,229	,470**	,424*	,472**	0,321	,391*	0,232	0,31	0,228	,376*	0,22
somatic complaints	,496**	,486**	,461*	0,361	,368*	,498**	0,177	,419*	0,316	,397*	0,291
social problems	,519**	,670**	,626**	,662**	,536**	,606**	,441*	,609**	,466**	,557**	,455*
thought problems	,381*	,392*	0,329	,434*	,511**	,567**	0,293	,409*	0,258	,493**	0,327
attention problems	,854**	,711**	,661**	,707**	,821**	,870**	,626**	,873**	,593**	,834**	,724**
rule-breaking behavior	,563**	,567**	,580**	0,204	0,311	,424*	,463**	,486**	,384*	,530**	,362*
agressive behavior	,901**	,698**	,753**	,386*	,573**	,633**	,554**	,818**	,626**	,704**	,613**
internalizing	,405*	,658**	,581**	,602**	,449*	,527**	0,304	,471**	,427*	,425*	,418*
externalizing	,743**	,586**	,634**	0,344	,536**	,570**	,640**	,742**	,490**	,673**	,549**

* Correlation is significant at the 0.05 level, ** Correlation is significant at the 0.01 level,1 Emotional Control, 2 Working memory, 3 Plan/Organize, 4 Organization of Materials, 5 Behavior Regulation Index, 6 Metacognition index, 7 Global Executive Composite

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Discussion

Much of what is known about executive and behavioral functioning in children with epilepsy is based on research focused on mainly temporal lobe epilepsy or different types of epilepsy. To our knowledge, our study is the first wherein parents and teachers provided information on executive as well as behavioral functioning in children with (frontal lobe) epilepsy. From a clinical perspective it is useful to have reliable and valid parent and teacher rating measures of the child's behavior and executive functioning. Therefore, the BRIEF (both for parents and teachers) and the CBCL and TRF were used, as they are all considered valid measurements for epilepsy patients [36,44].

Overall about 25 to 35 percent of the sample scored in the abnormal range of both indices of the BRIEF and the two main problem scales of the CBCL and TRF. Thus, executive and behavioral functioning appears to be impaired in many children with FLE. These findings are consistent with other studies using the BRIEF [30–32] and the CBCL/TRF [34,35] in children with epilepsy. This might suggest that children with FLE don't differ on executive and behavioral function compared to other epilepsies. However, comparison on subscale level might reveal differences. Unfortunately in other studies subscale ratings are mostly missing. Only 10 to 20 percent of our group was rated as having anxiety and mood problems on the CBCL/TRF. This is inconsistent with previous studies on children with epilepsy, which gave higher ratings. A possible explanation for this inconsistency is that lateralization might influence these problems. Most studies focus on lateralization of cognitive domains with language being the most studied function and there are few studies available about lateralization of behavior. Indeed, mood and anxiety disorders are associated with different functional activation and/or structural volume abnormalities in the left hemisphere [see for instance 52,53]. Neuroimaging studies show that psychopathology (e.g. depression) and temporal lobe epilepsy (TLE) seem to share similar neural networks [54,55]. This suggests a close interplay of structural and functional disruptions in TLE [56] as also suggested in FLE [12]. Thus, an epileptic focus in the temporal area might lead to more mood and anxiety problems. Swinkels, Kuyk, van Dyck and Spinhoven [57] do conclude in their review that prevalence of psychiatric problems in epilepsy patients ranges between 20 to 80%, in which TLE is the most studied focal epilepsy. In our study, the epilepsy variables age of onset, lateralization, drug load and duration of epilepsy had only a small and scattered contribution limited to some dimensions of the CBCL, TRF and BRIEF teacher. Children with left sided FLE did show more problems than children with bilateral or right sided FLE. One previous study [58] reported more behavioral problems in children with a right sided focus, in contrast to the present study. Whether specific behavioral problems can be linked to localization at all remains to be seen. Overall, current study suggests that children with FLE encounter less mood and anxiety problems than, as extensively reported in the literature, children with other epilepsies [for instance 4,5,11]. They show executive dysfunction in daily life to the same level. Parents and teachers ratings were moderately to highly correlated. Compared to parents, teachers tend to report more problems on the BRIEF. Other studies, also in other pathological contexts, show similar results [30,59,60], suggesting differences in executive function demands across settings. For the CBCL/TRF, parents reported more problems than teachers, which might be explained by a within- item disagreement [61,62]; parents and teachers often provide different ratings. Parents, however, reported more attention problems than teachers. Our findings concurred with the finding of Sherman et al. [63], but is inconsistent with other findings [see for example 35]. Two reasons why the two opinions might differ are that parental ratings can be affected by factors related to caregiver burden, leading to a response bias for behavioral problems [11,63,64] and an increase in behavioral problems [11]. Also, parental vigilance of seizures or medication-related cognitive and behavioral changes bias the parents perspective of attentional lapses or behavioral dyscontrol [63]. Conversely, due to the classroom setting, teachers can miss attentional lapses.

Ratings on the BRIEF and the CBCL and TRF are moderately to highly correlated, even in our small sample, suggesting a strong link between executive and behavioral functioning. The link was most pronounced in the teacher ratings. Comparing teacher with parent ratings, it appeared that behavioral regulation problems seem to be strongly linked to social and emotional problems at home. At school, our results suggest a strong link between increasing metacognitive problems and externalizing behavior. As mentioned before, the difference in EF demands across settings might explain this; parents report more behavioral regulation problems, whereas teachers reported more metacognitive problems. The domain ‘attention problems’ of the CBCL and TRF is most related to all scales of the BRIEF. This is not surprising. Attention problems, Attention-deficit/ Hyperactivity Disorder (DSM-5) in particular, are frequently reported in epilepsy [63-69] and are generally associated with executive dysfunction [see for example 70] and is a seen as a frontal lobe function.

There are several limitations to this study; First, the sample size is relatively small causing limited statistical power and there might be a selection bias due to our setting as a tertiary referral centre. Therefore, caution should be taken before generalizing these results to a larger group of children with FLE. Second, epilepsy severity and sleep quality can influence executive and behavioral functioning [27-29]. In the present study some of the children also experienced nocturnal seizures. Although sleep problems are embedded in the subscale ‘somatic problems’ of the CBCL/TRF this is not a reliable instrument for measuring sleep quality. We therefore suggest that future research specifies seizure severity and monitors sleep quality. Furthermore, a control group with another epilepsy classification would be instructive. The impact of parental stress and reporting bias on the results remains unknown, but may also contribute [71].

Conclusions

The whole range of executive dysfunctioning is linked to behavioral dysfunctioning in FLE, but ratings vary across settings and informants. Globally parents as well as teachers report executive dysfunction and behavioral problems to the same extent in about a third of this group. Common comorbidities such as anxiety and depression are relative sparsely reported in children with FLE and epilepsy variables have only a small and scattered contribution. Attention problems are highly associated with executive dysfunctioning. These results may have implications for interventions at home and in school: interventions based on executive dysfunction instead of treating the problematic behavior might reduce behavioral problems [72]. To our knowledge this is the first study exploring the relationship between the BRIEF and the CBCL/TRF in children with epilepsy, specific FLE. It is recommended conducting this on a larger clinical population in order to develop interventions.

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CHAPTER 4

The burden of parenting children with frontal lobe epilepsy

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Abstract

Objective: Caring for a childwith a chronic illness adds stress to the typical parenting stress in healthy developing children. This stress can place a heavy burden on parents andmay increasewhen a child displays problembehavior. In general, parenting and child's behavior problems are associated. Furthermore, externalizing (more outgoing) behavior is reported frequently in childrenwith frontal lobe epilepsy (FLE). Therefore, in this study, we first
investigated the burden of parents of childrenwith FLE, and second,we investigated the relation between the experienced burden and reported behavioral problems. The validity of parents' reports on proxy measures as well as duration of epilepsy is taken into account.

Methods: Thirty-one parents of childrenwith FLE completed validated questionnaires about behavioral problems and burden of parenting. To examine if parents tend to be inconsistent or unusually negative, we used the two validity scales of the Behavioral Rating Inventory of Executive Function (BRIEF) (Negativity and Inconsistency). Results: Only parents of children with FLE who have had epilepsy for 5 years or longer report more problems on
the Nijmeegse Vragenlijst voor de Opvoedingssituatie (NVOS) subscales 'Able to manage', 'Child is a burden', and 'Good Interaction' compared with the healthy controls. The subscale 'Child is a burden' significantly predicts scores in about 20% to 49% on the main scales of the Child Behavior Checklist (CBCL), the Global Executive Composite (GEC), and Behavioral Regulation Index (BRI) of the BRIEF. Only 6% of parents scored in the clinical range of the negativity scale of the BRIEF. For the inconsistency scale, this was 45%. Conclusion: Parents of children with FLE do not report excessive parental burden. Longer duration of epilepsy might be a risk factor in experiencing burden. The findings suggest a link between parental burden and behavioral problems in children with FLE. Externalizing behavioral problems are the most marked behavioral problems, which relate to the parental burden. Parents tend to be inconsistent in their ratings.

Introduction

Childhood chronic illness often impacts the entire support system [1,2], which in return influences health and health outcomes of children [e.g. 3]. Parenting stress is a key issue [1,4-7].

Family factors are recognized to be strong predictors of behavior problems in children with epilepsy [8-10], for instance, parenting style [8-12], and caregiver psychopathology [13].

Epilepsy related factors that have a role in the development of parental stress are the uncertainty about seizure occurrence, potential complications and uncertainty about long-term outcome [14,15]. The comorbid cognitive disabilities [16-18] may also contribute [15,19-22]. Further, health care issues have been mentioned, such as seizures management, clinic visits, health decline and hospitalizations. Lifestyle issues to maintain seizure control, for example sleep management and restricted family activities, may also contribute to the parents burden.

Lastly, children's behavioral problems are an important factor leading to parental stress and depression [1,8,23]. These behavioral problems are more common in epilepsy than in other chronical conditions [14,24-30] and might be caused by the underlying brain pathology and its dynamics [31-33]. A predisposition for developing behavioral problems [34], and even a bidirectional relationship between behavioral disorders and epilepsy have been suggested [35,36].

In sum, epilepsy affects parenting and a child's behavior, leading to parenting stress and burden. This in turn affects the child's behavioral problems (figure 1).

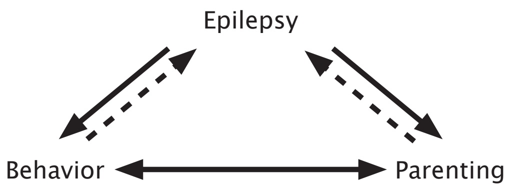

Figure 1: bidirectional relationship

It could be argued that behavior as well as parenting might interact with epilepsy factors. Different definitions of burden (or family stress) have been proposed in the literature and they all emphasize the effect (living with) a patient has on the family. We operationalize the parental burden in this study as added stress on the parent and family caused by the pediatric chronic illness. This is an additional challenge to the typical parenting role, which naturally presents occasional stressors throughout development [37].

Externalizing behavioral problems are often reported in children with FLE [e.g. 38,39]. This is in contrast to the marked internalizing behavioral problems in focal temporal seizures [9,10]. Focal frontal seizures are associated with nocturnal seizures [40-42] and possible executive dysfunction [43,44], which are related to behavioral problems [e.g. 44]. Furthermore, it is assumed that externalizing behavioral problems place a greater burden on the caregiver [45,46]. Therefore, the aim of the present study is twofold. First, we want to investigate the burden of parents of children with frontal lobe epilepsy (FLE). This subject has not previously been investigated in this group and is of general interest as it is relevant to the clinical practice in order to develop adequate interventions.

Second, we aim to investigate the relationship between the experienced burden and reported behavioral problems. Additionally, we will explore the difference between more externalizing (outgoing) behavior and more internalizing (introvert) behavior in relation to the experienced burden. Most research is based on parent and/or teacher-proxy measures. An instrument often used and validated in the field is the child behavior checklist (CBCL) [24,25,47-49]. As responses of caregivers may be inaccurate or exaggerated [9-11,14,28,50-53], also due to parenting stress, the validity of parent proxy measures might be questioned. For this reason, validity of parents' reports on proxy measures will be taken into consideration. Lastly, most epilepsy variables do not seem to be of much influence on cognitive development [e.g. 38]. However, studies show that longer duration of epilepsy might be considered a risk factor for developing psychopathology [e.g. 44]. As children's behavioral problems can lead to parental stress, duration of epilepsy might also be a risk factor for increased parental burden. Therefore, we will also investigate duration of epilepsy in relation to parental burden.

Methods & Materials

Sample

This study was part of a larger study concerning executive and behavioral functioning in children with FLE. For this study all children aged 8 to 12 years with a confirmed diagnosis of FLE were referred by the paediatric neurologist between January 2013 and January 2015 for assessment to the psychology department of our tertiary epilepsy centre. Some of these children were referred because parents reported cognitive and/or behavioral problems, but a large proportion was referred on behalf of this study. Children with frontal lobe epilepsy who were assessed prior to January 2013 and who met the inclusion criteria were invited to participate also. There were 5 children of 7 years old included because they almost turned 8. Parents completed questionnaires concerning the burden of parenting and perceived behavioral problems while children were being tested. As all included patients were Dutch native speakers, all communication was done in Dutch and all questionnaires were validated in Dutch.

The diagnosis focal frontal epilepsy was based on the International League Against Epilepsy criteria and confirmed by an EEG recording. The frequency of seizures was unfortunately unknown, partly because a large part of the sample experienced nightly seizures, which are difficult to detect.

Inclusion criteria were age between 8 and 12 because assessment of executive functioning with validated and normative tests is possible from the age of eight. Besides, executive function demands differ in primary and secondary education and in the Netherlands children attend secondary education from approximately age twelve. Moreover, previous work [54] has shown significantly poorer performance in children with FLE aged 8-12 years compared to other children with other epilepsies. Other inclusion criteria were IQ > 70 or school achievement scores above C level (Dutch CITO) in math and language in order to understand test assessment. We excluded children with psychiatric problems, which could influence test assessment, meaning not being cooperative or having problems adjusting to the test structure, except for attention deficit and hyperactivity disorder (ADHD), which is common in children with epilepsy [55].
The study was approved by the Ethical Committee of MST Enschede and parents gave their informed consent.

Measures

Parents' burden

The main scale A with 8 subscales (see table 1) of the Dutch questionnaire Nijmeegse Vragenlijst voor de Opvoedingssituatie (NVOS) [56] was used to measure the burden of parents. This scale represents only the experienced burden. Internal consistency and test-retest reliability are good [56]. The questionnaire is validated with different control groups. The manual of the NVOS shows normative data for the different scales in the main subscales for several norm groups. Our group was only compared to a healthy control group.

Behavior problems

Parents completed the Child Behavior Checklist (CBCL) [49] and the Behavioral Rating Inventory of Executive Function (BRIEF) [57] (table 1). This analysis focuses on the externalizing and internalizing scale of the CBCL and the two main indices (Behavioral Regulation index (BRI) and Metacognition index (MC)) and general index (Global Executive Composite (GEC) of the BRIEF.
The BRIEF has good psychometric properties that include appropriate construct validity. Internal consistency is strong and the test-retest reliability is also high [58]. The validity of the parent scores was explored using the two validity scales of the BRIEF: ,"Negativity," and ,"Inconsistency,". The first estimates whether responses are given in an unusually negative way. The latter estimates whether responses are inconsistent. A 'Negativity' and 'Inconsistency' score ≥ 5 is considered statistically significant. A score 1.5 SD (≥ percentile 93) above average is considered statistically significant for the indices.
The CBCL is a well-established behavioral questionnaire with good psychometric properties [49], also for children with epilepsy [48]. A score 1.33 SD (≥ percentile 90) above average is considered statistically significant for the main scales.

Table 1: Test protocol

Test	Description
Nijmeegse Vragenlijst voor de Opvoedingssituatie (NVOS)	A questionnaire to assess burden of parenting and attributions towards parenting. It comprises four main scales all consisting of subscales. In this study we only use main scale A, which consists of eight subscales (5 point Likert scale): 1. Acceptation (4 items) 2. Able to manage (8 items) 3. Experience problems (7 items) 4. Want to change situation (6 items) 5. Child is a burden (7 items) 6. Being in it alone (4 items) 7. Having fun (5 items) 8. Good interaction (5 items) All subscales are added up, converted into standard scores and compared to average scores of the norm groups.
Behavior Rating Inventory of Executive Functions (BRIEF)	A norm-referenced parent-report measure of the child's executive function. It contains 75 items (score 'never', 'sometimes', 'often') in eight non-overlapping clinical scales and two validity scales. These theoretically and statistically derived clinical scales, form two indexes, both consisting of subscales: 1. Behavioral Regulation Index: Inhibit (10 items, Shift (8 items) and Emotional Control (10 items); 2. Metacognition Index: Initiate (8 items), Working Memory (10 items), Plan/Organize (12 items), Organization of Materials (6 items) and Monitor (8 items). All scores form the Global Executive Composite which takes into account all of the clinical scales and represents the child's overall executive function. The two validity scales (Negativity and Inconsistency) are used to determine if parental scores can be reliably calculated. The negativity scale is calculated by adding up the answers with a maximum score in this specific scale. The inconsistency scale is calculated by adding up 10 so-called 'different scores' between two items.
Child Behaviour Checklist (CBCL)	A parent report questionnaire of 118 items to rate a child on various behavioral and emotional problems from 0 (absent) to 2 (often). It is made up of two higher order factors: internalizing and externalizing: 1. Internalizing Problem Scale 2. Externalizing Problem Scale

Statistical analysis

Data were analysed using the Statistical Package for Social Sciences (IBM SPSS Statistics 23.0). The data were compared with normative data of the Dutch population. To explore group differences based on duration of FLE, children were categorized into short (< 5 years) vs long (≥ 5 years).

Data of the NVOS were calculated and compared to the normative data. Effect sizes for this data are shown using cohen's *d*.

The association between the NVOS and the behavioral scales was investigated with the Spearman's rank-order correlation. Simple univariable and multiple regressions were used to evaluate the relationship between the NVOS scores and the scores on the behavioral scales. To differentiate between 'outgoing behavior' and 'introvert behavior' we grouped the externalizing scale of the CBCL and the BRI of the BRIEF for outgoing behavior and the internalizing scale of the CBCL and the MC of the BRIEF for introvert behavior.

Results

A total of 31 children met the inclusion criteria (table 2). Five of these children had a confirmed ADHD diagnosis.

Table 2: Demographic and epilepsy variables

Characteristics	Value
N	31
Patients	
– Gender (male:female)	18:13
– Mean age (±SD) in years at assessment	9.2 (±1.6)
– Range (years)	7–12
Duration of epilepsy	
– Mean duration (±SD) in years	4.5 (± 2.7)
– Range (years)	1–9
– Short duration (< 5 years)	18 (58%)
Seizure focus based on EEG	
– Left frontal	10 (32%)
– Right frontal	6 (19%)
– Bifrontal	11 (34%)
– Frontal, but unknown lateralisation	4 (13%)
Anti epileptic drugs	
– Monotherapy	12
– Polytherapy	16
– None	3

Nijmeegse Vragenlijst voor de Opvoedingssituatie

Mean NVOS scores were calculated for our group and compared with a healthy control group. Table 3 shows that overall parents of children with FLE did not express more-than-average parental burden. Table 3 also indicates that parents of children who have had epilepsy for 5 years or longer reported more problems on the NVOS subscales 'Able to manage', 'Child is a burden' and 'Good Interaction' compared to the healthy controls. Parents of children who have had epilepsy shorter than 5 years expressed average scores.

The correlations of the subscales of the NVOS with all subscales of the behavioral questionnaires are shown in table 4. Correlations between almost all NVOS scales and the externalizing scale of the CBCL are high. There are no correlations between all NVOS scales and the MC index of the BRIEF. Correlations between the NVOS scales and the BRI index of the BRIEF are small to high.

Because our sample size is small and internal correlations of about a third of the subscales of the NVOS are high ($r_s. \geq .70$, $p \leq .000$), we only used subscale 'Child is a burden' of the NVOS for the regression analysis (table 5). 'Child is a burden' significantly predicts scores on the Internalizing (20%) and Externalizing (37%) scales of the CBCL, the GEC (25%), BRI (49%) and negativity score (24%) of the BRIEF. It also explains a significant proportion of variance in those scores.

Table 3: NVOS scores in relation to healthy controls

	Healthy control group		Total FLE group			Duration epi > 5 years			Duration epi < 5 years		
Scale	*M* HC	*SD* HC	*M FLE*	*SD FLE*	*d*	*M FLE > 5*	*SD FLE > 5*	*d*	*M FLE < 5*	*SD FLE < 5*	*d*
Acceptation	1.40	.49	1.41	.59	.02	1.39	.53	–.02	1.41	.65	–.02
Able to manage	1.71	.56	1.81	.62	.17	1.91	.70	.32	1.74	.57	–.05
Experience problems	1.94	.60	2.04	.65	.16	2.09	.56	.26	2.00	.72	–.09
Want to change situation	1.71	.60	1.66	.69	–.07	1.83	.74	.18	1.54	.65	.27
Child is a burden	2.01	.70	2.30	.89	.36	2.45	.85	.66	2.20	.93	–.23
Being in it alone	1.88	.75	1.76	.75	–.16	1.82	.69	–0.08	1.71	.81	.22
Having fun	1.57	.53	1.46	.53	–.21	1.68	.53	.04	1.37	.52	.38
Good interaction	1.76	.65	1.85	.62	.14	2.00	.66	.36	1.73	.59	.05

d = cohen's *d*
HC= healthy controls
FLE= frontal lobe epilepsy patients

Table 4: Correlating NVOS with behavioral scales

Behavior scales / *Subscale NVOS*	Int CBCL	Ext CBCL	Total BRIEF	BRI BRIEF	MC BRIEF	NEG BRIEF	INC BRIEF
Acceptation	.11	.26	.18	.26	.05	.16	.12
Able to manage	.38*	.72***	.35	.35	.05	.17	.05
Experience Problems	.18	.56***	.36*	.37*	.09	.22	.09
Want to change situation	.41*	.71***	.42*	.57**	.02	.30	.14
Child is a burden	.43*	.66***	.60***	.70***	.19	.51**	.16
Being in it alone	.30	.41*	.22	.40*	.06	.26	.08
Having fun	.39*	.54**	.41*	.37*	.07	.32	.14
Good interaction	.43*	.63***	.22	.26	.06	.24	.14

Correlation displayed as Spearmans r_s
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$
Int=internalizing, Ext=externalizing, MC=metacognition index, neg=negativity scale, inc=inconsistency scale

Table 5: Regression analyses 'Child is a burden'

Subscale	R^2	*F (1,29)*	*p*	*t (29)*	*β*
Int CBCL	.20	7.04	.01	2.65	.44
Ext CBCL	.37	17.24	.00	4.15	.61
GEC	.25	9.70	.00	3.11	.50
BRI	.49	27.54	.00	5.25	.70
MC	.03	.94	.34	.97	3.56
Inc	.02	.65	.43	.81	.27
Neg	.24	10.23	.00	3.20	.51

Int=internalizing, Ext=externalizing, GEC=global executive composite, BRI=behavioral regulation index, MC=metacognition index, inc=inconsistency scale, neg=negativity scale

Child Behavior Checklist and Behavioral Rating Inventory of Executive Function

Overall, parents reported significantly elevated problems in about 12% to 34% of the sample on all behavioral scales. Only 6% of the parents scored in the clinical range of the negativity scale of the BRIEF. For the inconsistency scale the percentage of parents who scored in the clinical range was 45% (figure 2). Parents of children with epilepsy more than 5 years did not report significantly more behavioral problems on all different behavior scales compared to parents of children with epilepsy shorter than 5 years (lowest $p > .07$).

Multiple regressions were run 1) to predict 'Child is a burden' based on 'outgoing behavior' and 2) to predict 'Child is a burden' based on 'introvert behavior'. A significant equation was found for 'outgoing behavior' ($F(2,28)= 17.21$, $p = .00$), with an $R^2 = .55$. The BRI of the BRIEF significantly predicted scores on 'Child is a burden' ($b = .53$, $t(28) = 3.34$, $p = .00$).

The Externalizing Scale did not add significantly to 'Child is a burden' ($b = .30$, $t\ (28) = 1.88$, $p = .07$). For 'introvert behavior' a small significant equation was found ($F(2,28) = 3.88$, $p =.03$) with an $R^2 = .22$. The Internalizing Scale significantly predicted scores on 'Child is a burden' ($b = .44$, $t\ (28) = 2.63$, $p = .01$). The MC of the BRIEF did not add significantly to 'Child is a burden' ($b = .15$, $t\ (28) = .88$, $p = .38$).

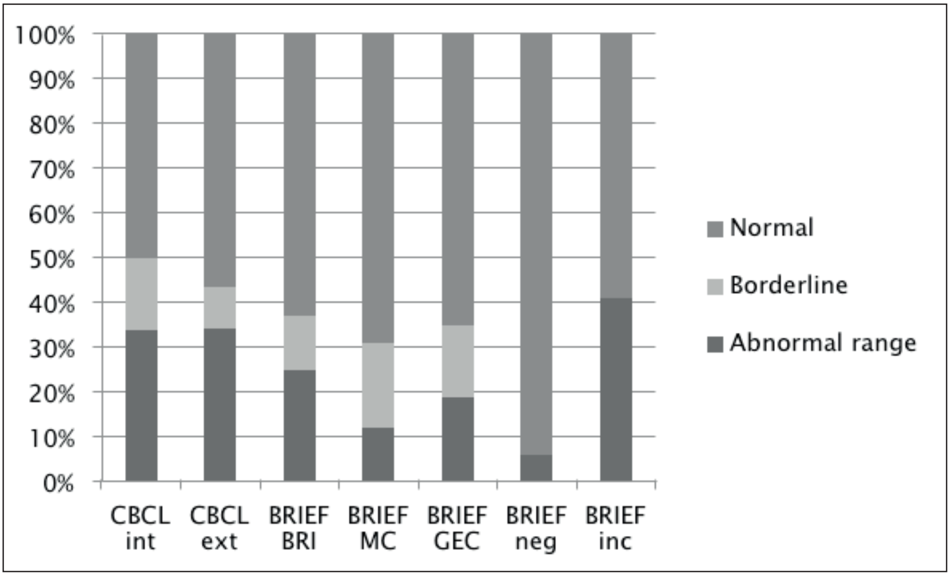

Figure 2: Results behavioral questionnaires

Discussion

We assessed the burden of parents of children with FLE. Overall, parents did not report more burden in comparison to the normative reference sample. However, parents of children with enduring epilepsy for more than 5 years did report more burden. These parents also experienced more problems in parenting, had difficulty to manage the problems and interaction between parent and child was experienced as inadequate. These results might implicate that duration of epilepsy could be a risk factor for experiencing more burden in parenting. In this specific group with enduring epilepsy, the intractability of the epilepsy [1] and nocturnal seizures (and partly also poor quality of sleep), over a longer period of time may impact the family system [59,60] leading to exhausted parents. This can account for, at least a part of, the experienced burden. Surprisingly, the parents of children with enduring epilepsy did not report more behavioral problems compared to parents of children with a shorter duration in this study. This is surprising because it might be expected that these parents would report more behavioral problems [61-63]. In general, the demands on executive function, a frontal role, increases with brain maturation [64]. In FLE especially, structural and functional disorders as well as epileptic discharges, interfering with physiological brain circuitry, may lead to executive dysfunction emerging over time [38,65] resulting in long-term developmental ‚"lagging behind," [38,66,67]. This cognitive delay and comorbid (behavioral) problems is known to place a burden on parents in general [e.g. 21,22,68], but in our small sample it does not lead to more reported behavioral problems.

Our analyses suggest that self-reported parental burden is linked to reported outgoing/externalizing behavior especially, which concurs with other reports [45,46]. The findings are valid as far as the BRIEF negativity scale is concerned: responses of only six percent of the parents were unusually negative. However, almost 50 percent of the parents tended to be inconsistent in their ratings. Consequently, parents' reports should be cautiously interpreted. It should be noted that these validity scales pertain to the BRIEF only. This type of problem with validity in proxy measures is the so-called response inconsistency and can be caused by multiple factors [e.g. 69,70]. The inconsistency in our parents group might be explained by the fact that children with epilepsy show huge variation in their behavior and cognitive skills causing behavior difficult to rate. Furthermore, parents do not compare their children to healthy children but rate their children according to the circumstances. The latter meaning that parents might find that children are doing well at least in some situations despite their epilepsy. This could also explain the somewhat unexpected relatively low scores on the behavorial questionnaires, especially in the group with enduring epilepsy. All in all, inconsistency of parent ratings addresses an important issue, which is in need for further research.

It could be argued that there is a bidirectional effect between parental burden and behavioral problems in children with FLE as it is common for epilepsy in general [8-12]. There were significant correlations between the behavioral scales and the experienced burden. These were high for more outgoing behavior, a feature more pronounced in children with FLE [38,39]. Moreover, experiencing that the child is a burden seems to predict behavioral scores (especially more outgoing behavior) and vice versa,. These findings could strengthen the hypothesis that there is a bidirectional effect between parental burden and perceived behavioral problems. Further research in this area is needed.

There are a number of limitations in this study that has to be acknowledged. Our study is firstly limited by a relatively small sample size and the lack of a control group. The study explores a specific group, FLE, but there is still heterogeneity of the sample with respect to seizure type and underlying pathology. As this study is part of a larger study in which children were referred for test assessment, children with health or psychiatric problems, which could influence test assessment, were excluded. Consequently, parents of children with many behavioral issues may not have completed the questionnaires. Therefore, it could be argued that the current sample is not fully representative for children with FLE. However, it should be noted that a part of our sample did not have a psychiatric diagnosis, but would meet the criteria for one. These children were not seen by a psychiatrist and were not given any diagnosis, because a part of the behavior was linked to their frontal disturbances. For future research this needs to be taken into consideration.

Secondly, the NVOS is rarely used in clinical groups and ecological validity may be questioned. Despite this, the high correlations of the NVOS with the CBCL and the

BRIEF make it worthwhile to consider it more often for clinical use. The present study suggests a link between behavioral problems and caregivers' burden, as is suggested for epilepsy in general. This subject has not been investigated in this population systematically. The NVOS could potentially be a good questionnaire to measure this.

Lastly, we used the negativity scale and the inconsistency scale of the BRIEF to interpret ratings of other questionnaires. They are designed for the BRIEF, the generalizability to other ratings has not been investigated yet. Therefore, at this moment, scores on these scales can only be used to examine a possible tendency of negativism or inconsistency.

In clinical practice, the use of questionnaires related to parental burden and stress is advisable, since there seems to be a bidirectional relationship between behavioral problems and the burden as experienced by parents in children with epilepsy. Interventions based on this burden can also have substantial implications; treating and/or educating parents might diminish behavioral problems as well as the experienced burden. In addition, longer duration of epilepsy is considered a risk factor for developing psychopathology [8,23]. Hence, early intervention might help reduce psychopathology in children with FLE in the long term [71]. As the validity of parental reports can be questioned, other ways of obtaining information about a child's behavior and interaction with parents is encouraged. Developing a validity tool, such as The Structured Inventory of Malingered Symptomatology (SIMS; 72), for parent proxy measures is recommended. An issue that remains unknown at this time is the relation between parental burden and epilepsy (variables) itself. In general, the impact of epilepsy variables is not as clear as one might expect, as strong relationships between these variables and behavior are missing [41,73,74]. In future studies it is worthwhile to explore these issues.

In sum, these findings suggest that parents of children with enduring FLE experience more parental burden. Furthermore, there seems to be an association between parental burden and behavioral problems in children with FLE, with more outgoing behavioral problems being the most pronounced. The inconsistency of the proxy reports is high and could make parental report less reliable.

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4

PART II: COGNITION

CHAPTER 5

Working memory in pediatric frontal lobe epilepsy

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Abstract

Thirty-two children with frontal lobe epilepsy (FLE) were assessed using different working memory measures. In addition, parents and teachers completed the working memory scale of the Behavioral Rating Inventory of Executive Functioning (BRIEF) to assess the children's "daily life behavior". Results suggested minimal working memory deficits as assessed with performance-based measures. However, the BRIEF showed more working memory deficits suggesting that, on a daily life level, working memory problems seem to be associated with FLE. We discuss why the results of the performance-based measures are not consistent with results of the BRIEF.

Introduction

In general, cognitive and learning problems are common in children with epilepsy [e.g. 1,2]. Findings are based on populations with different types of epilepsy; over recent years frontal lobe epilepsy (FLE) has been increasingly investigated, but it is still not well represented in research publications [3-8]. This is undesirable since FLE is the second most common type of focal epilepsy, causing 20 to 30 percent of all focal seizures [9], with an average age at onset ranging from 4.6 to 7.5 years [10].

To date, only five review articles have been published on cognition in FLE, and they suggest that cognition is compromised [8,10-13]. The impact of epilepsy variables (age at onset, duration of epilepsy, lateralization, and medication), however, is still debated.

So far, most empirical studies have focused on adult populations with FLE; most of the few studies conducted in children with FLE lack statistical power. Consequently, there is a need for cognitive research on FLE in children.

The present study focuses on working memory, which is an important aspect of executive functioning (EF), considered to be a frontal lobe function. Working memory is key in both academic settings and daily life [14] and is associated with IQ performance [see also 15]. Many definitions of working memory are available [16-18]; for this study we used the 2013 definition [19]: "the ability to hold in mind and mentally manipulate information over short periods of time."

There are three reasons why studying working memory is important in children with FLE. Firstly, many children with FLE and normal intelligence have learning difficulties [20-22]. This could be related to their compromised working memory [23,24], because working memory problems are often associated with learning problems [14,25- 29]. Secondly, working memory is linked to a network of prefrontal and parietal areas [30,31-33]. Neuroimaging studies suggest that FLE might lead to structural and functional disorders [10,34] as seizures, as well as interictal epileptic discharges, are increasingly recognized as interfering with physiological brain circuitry [10,34,35). An epileptic focus in the frontal network could therefore lead to executive function problems, including working memory problems [36]. Thirdly, recent studies report working memory deficits in groups with different types of epilepsies [15,24,37,38] and relate this to behavioral problems [38]. Furthermore, some studies suggest that auditory working memory is compromised in people with FLE [21] while research on visual working memory is lacking. The visual domain can act alone, but can also interact with the verbal domain and is thought to be located in different areas of the brain [39]. Surprisingly, one study [15] found no association of FLE with working memory problems, although other types of epilepsy did show working memory problems. Earlier studies showed that performance-based measures were associated with isolated cognitive deficits in children with epilepsy [e.g. 1,2]. Behavior in daily

life, however, is reflected more by subjective measures such as the Behavioral Rating Inventory of Executive Functioning (BRIEF) [40,41]. Only a few studies have addressed the relationship between tested and reported information about EF in children with epilepsy [42–44].
As suggested by others [24,44], we studied working memory using clinical tests and combined these with a questionnaire about daily life behavior: the working memory scale of the BRIEF for parents as well as teachers. The BRIEF was recently studied in this population for the first time [45]. The aim of the current study was to increase the knowledge about working memory in children with FLE, because this may be relevant for the development of intervention strategies [46]. We hypothesized that children with frontal epilepsy would score lower on working memory tasks overall compared with the normative reference group. Secondly we hypothesized that parents and teachers would report working memory problems in daily life behavior. Thirdly, we hypothesized that teachers would report more problems in the BRIEF than parents, because of the differences in executive function demands in various settings.

Materials & Methods

Participants

Children with FLE were referred by neurologists for a broad neuropsychological assessment. The definition of the type of epilepsy was based on the International League Against Epilepsy criteria and confirmed by an EEG registration. The assessment of executive functioning with validated and normative tests is possible from the age of eight. Further executive function demands differ in primary and secondary school; in the Netherlands children go to secondary school at approximately twelve years old. Previous work [23] has shown significantly poorer performance in children with FLE aged 8–12 years compared to other children with other epilepsies. Inclusion criteria were therefore children aged between 8 and 12 with a diagnosis of frontal lobe epilepsy and IQ $>$ 70 or school achievement scores above C level (Dutch CITO) in math and language. Exclusion criteria were health and/or psychiatric problems, which could influence the neuropsychological assessment, apart from attention deficit and hyperactivity disorder (ADHD) which is very commonly diagnosed in children with epilepsy [47]. Because of the small group, we also enrolled 7-year old children who would soon be 8, one 6 year old and one 12 year old. A total of 32 children (18 boys, 14 girls) met these criteria. Five had a confirmed ADHD diagnosis. For several reasons, the full protocol was not applied to all individuals (see table 1). A few children refused to finish some tasks; one child did not complete all tasks, but the child's parents completed the questionnaires.

Procedure

As part of a broad neuropsychological assessment routine undertaken by a psychology assistant, working memory was assessed using visual and verbal recognition tasks, with serial as well as simultaneous presentations of the FePsy, a computerized test battery [48]. The Digit Span of the WISC-III-NL was used to assess auditory working memory. Executive function behavior in daily life was assessed with the working memory scale of the BRIEF, parent and teacher form [40,41]. Table 1 shows the details of the tests. The study was approved by the Ethical Committee of MST Enschede, and parents gave their informed consent.

Statistical analysis

The data, corrected for age, were compared with normative data from the Dutch population. A score 2SD below average on the digit-span of the WISC-III-NL and the FePsy tasks was considered statistically significant and suggests a deficit in this domain. In the FePsy, the normative reference group is divided into two groups: older and younger than 10 years, and in the WISC-III-NL, the Digit Span is divided into four age groups. For the BRIEF a score of 1.5 SD (≥ percentile 93) above average was considered statistically significant and suggests executive function problems. Differences in normally distributed neuropsychological test results and scores on the questionnaire between the FLE cohort and the reference values were tested using one sample t-tests at a 5% significance level. To explore group differences based on epilepsy variables, children were categorized into left vs right vs bifrontal lateralization (based on EEG), age at seizure onset (young < 5 years vs old ≥ 5 years), duration of FLE (short < 5 years vs long ≥ 5 years) and drug load (monotherapy, polytherapy, none). Severity of the epilepsy was not taken into account due to the unknown frequency of seizures, with most occurring at night. However, children were enrolled from a tertiary epilepsy centre, suggesting that their epilepsy is more difficult to treat. Imaging, where conducted, did not show lesions (apart from one participant whose scores were in the average range) or specific localizations; therefore no participant was a surgical candidate at the time. Correlation analysis were used to assess the relationship between all measures. Independent t-tests and ANOVA, and nonparametric tests in case of small numbers in subgroups, at the 5% significance level were used to compare the groups for continuous variables. Sample sizes were small, so effect sizes are shown when appropriate using cohen’s d. Data were analysed using the Statistical Package for Social Sciences (IBM SPSS Statistics 20.0).

Table 1: Test protocol

Test	N*	Description
*Visual WM***		
Fepsy:		
Corsi-block	29	Stimuli (starting with three blocks, up to nine) are presented with a presentation time of 1 second per item in a sequence digitally. After a delay the sequence has to be mimicked.
Recognition figures serially	25	Stimuli (four figures) are presented digitally serially during a learning phase with a presentation time of 1 second per item. After a delay of 2 seconds the screen shows one of these figures and the testee has to indicate the order of presentation. The number of correct items is scored, with a maximum of 24. Reaction time is measured in ms.
Recognition figures simultaneously	27	Stimuli (four figures) are presented digitally simultaneously during a learning phase with a presentation time of 4 seconds. After a delay of 2 seconds the screen shows one of these figures between distracters. The target items has to be recognized. The number of correct items is scored, with a maximum of 24. Reaction time is measured in ms.
*Auditory WM***		
Fepsy:		
Recognition words serially	29	Stimuli (four words) are presented digitally serially during a learning phase with a presentation time of 1 second per item. After a delay of 2 seconds the screen shows one of these figures and the testee has to indicate the order of presentation. The target items has to be recognized. The number of correct items is scored, with a maximum of 24. Reaction time is measured in ms.
Recognition words simultaneously	29	Stimuli (four words) are presented digitally simultaneous during a learning phase with a presentation time of 4 seconds. After a delay of 2 seconds the screen shows one of these words between distracters. The target items has to be recognized. The number of correct items is scored, with a maximum of 24. Reaction time is measured in ms.
Wechsler Intelligence Scale for Children: Digit span	28	Orally given sequences of numbers are asked to be repeated, either as heard of in reverse order.
Questionnaires		
Working memory Scale of the Behavior Rating Inventory of Executive Functions (BRIEF) parent (p) and teacher (t) form	32 (p) /30 (t)	This is a subscale of the Metacognition index. It consists of 10 items and measures a child's ability to hold information in mind with the objective of completing a task. Items include "Forgets what he/she was doing" and "Has trouble remembering things, even for a few minutes."

Results

The children's demographic characteristics and epilepsy variables are shown in table 2.

Test results

Mean scores for each age group were given in Figure 1.
For the word recognition only 10–16% of the participants (3–5 participants) showed impaired function. For the figure recognition 26–55% of the participants (8–17 participants) showed impaired function. For the digit span this could not be calculated due to missing standard deviation for the normative data.
Correlation between all performance based measures was low. Recognition Figures Serially correlated with Recognition Words Serially ($r = .61$, $p = .006$) and with Digit Span backward ($r = .49$, $p = .035$).

Table 2: Demographic and epilepsy variables

Characteristics	Value
N	32
Participants	
1. Gender (male:female)	18:14
2. Mean age (±SD) in years at assessment	9.2 ±1.6
Age at seizure onset	
3. Mean age (±SD)	4.6 ± 2.8 years
4. Younger age (< 5 years)	16 (50%)
Duration of epilepsy	
1. Mean duration (±SD)	4.6 ± 2.7 years
2. Short duration (< 5 years)	17 (53%)
Seizure lateralization based on EEG	
1. Left frontal	11 (34%)
2. Right frontal	6 (19%)
3. Bifrontal	11 (34%)
4. Unknown lateralisation	4 (13%)
AED treatment	
5. Monotherapy	12 (38%)
6. Polytherapy	16 (50%)
7. No AED	4 (12%)

Recognition Words Simultaneously correlated with Recognition Words Serially ($r = .46$, $p = .049$). Results from the participant group did not differ significantly from those of the reference group, apart from Simultaneously Presented Figures ($p < .001$ ($t(6) = -5.767$, CI [−7.04, −2.85]) and $p < .001$ ($t(19) = -8.516$, CI [–5.54, –3.36])) with large effect sizes (*d* = 1.76, *d* = 1.68) and Digit Span Forward (p = .002(CI [–2.67, –.83])) in the youngest group (Table 3). For the other tests, effect sizes ranged from very small to (low) medium.

Comparison between groups revealed no significant differences between left vs right vs bifrontal lateralization (based on EEG), age at seizure onset (young < 5 years vs old ≥ 5 years), duration of FLE (short < 5 years vs long ≥ 5 years) and drug load.

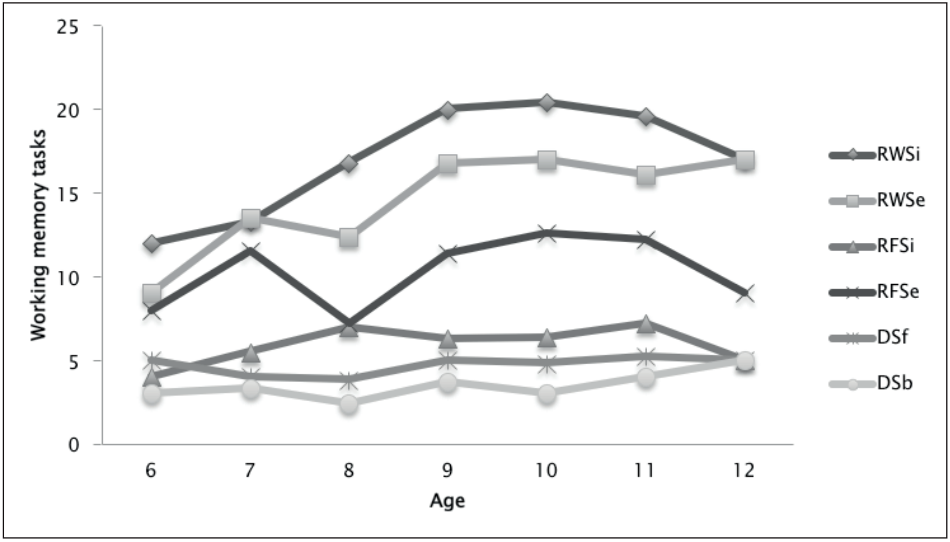

Figure 1: mean score age groups

The working memory scale of the BRIEF

There were no significant differences on the working memory scale ratings between parents and teachers. Table 4 shows that approximately 40 to 50% of the scores of both sources are above average (almost a third scored 1.5 standard deviations above average norms). Correlation between both BRIEF measures was high (r = .566 , $p < .001$).

Comparison between groups revealed no significant differences between left vs right vs bifrontal lateralization (based on EEG), age at seizure onset (young < 5 years vs old ≥ 5 years), duration of Frontal Lobe Epilepsy (FLE) (short < 5 years vs long ≥ 5 years) and drug load.

The working memory scale of the BRIEF for parents was only correlated with serially presented words (r = –.44, p = .026). For the teachers' scores the working memory scale was significantly associated with serially presented words (r = –.74, $p < .001$) and figures (r = –.65, p = .001).

Table 3: Neuropsychological scores: participants and the reference group

Test	N	FLE Participants' mean (±SD)	Reference mean (±SD)	Cohen's d	p-value
Corsi Block (CB)					
≤ 9 years	15	3.73 (±0.93)	4.24 (±0.55)**	.67	.051
> 9 years	14	4.75 (±0.79)	4.69 (±0.75)**	-.07	.779
Recognition figures serial (RFSE)					
≤ 10 years	18	10.4 (±3.8)	10.7 (±3.3)	.08	.737
> 10 years	7	11.7 (±5.1)	13.1 (±2.7)	.34	.498
Recognition figures simultaneous (RFSI)					
≤ 10 years	20	6.3 (±2.3)	10.7 (±2.9)	1.68	.000*
> 10 years	7	6.9 (±2.3)	11.8 (±3.2)	1.76	.001*
Recognition words serial (RWSE)					
≤ 10 years	21	14.8 (±4.2)	16.6 (±4.8)	.40	.091
> 10 years	8	16.3 (±6.6)	11 (±4.1)	-.96	.061
Recognition words simultaneous (RWSI)					
≤ 10 years	21	17.5 (±4.3)	16.6 (±5.0)	-.19	.336
> 10 years	8	19.3 (±6.6)	18.4 (±3.3)	-.17	.725
Digit-span forward (DSF) ***					
≤ 8 years	10	5.10 (±1.3)	6.85		.002*
9 years	6	6.67 (±1.4)	7.26		.336
10 years	4	7.00 (±1.8)	7.53		.602
11 years	8	7.00 (±2.1)	7.84		.303
Digit-span backward (DSB) ***					
≤8 years	10	3.2 (±1.2)	4.01		.067
9 years	6	4.5 (±1.0)	4.22		.542
10 years	4	3.8 (±1.7)	5.00		.239
11 years	8	4.63 (±2.1)	5.01		.614

* *p* = significant
** Reference group consists of only people with epilepsy
*** SD not available and therefore also no *d*

Table 4: Ratings working memory scale BRIEF

BRIEF working memory scale	N (%)
Parents' ratings	
<= percentile 83 (< 1SD)	19 (60%)
percentile 84-93 (1 SD)	3 (9 %)
=> percentile 93 (> 1,5 SD)	10 (31%)
Teachers' ratings	
<= percentile 83 (< 1SD)	15 (50%)
percentile 84-93 (1 SD)	6 (20%)
>= percentile 93 (> 1,5 SD)	9 (30%)

Discussion

This study explored the auditory and visual domain of working memory in children with FLE. Working memory, assessed with performance-based measures (FePsy and Digit Span), was not impaired with the exception of two minor parts: Simultaneously Presented Figures, and Digit Span Forward for children aged 7 and 8 years. This negative finding concurs with other studies in children with FLE [15,20,49]. Also, groups based on different epilepsy variables revealed no differences, which is consistent with previous studies [15,20,50-53]. The mean scores of the working memory tests in our small group show improving working memory across the age span, but this growth seems to levels off at around 11 years. An explanation for this could be that demands on executive function increases with brain maturation [54] and with frontal disturbances, executive dysfunction emerges over time [10,34] resulting in long-term developmental "lagging behind" or a delayed development of working memory, as previously suggested [23].
Preliminary findings in this same group and other studies on children with FLE imply that inhibition as well as shifting problems are more frequently found [55-57]. Also, attention problems are reported extensively in children with epilepsy [e.g. 47]. Besides, there is evidence that working memory seems to rely on the frontoparietal network and is not a frontal function per se [20,30,31] and might depend on motor control [58]. As the neuroanatomical basis of executive functions has been suggested to be in different cortical and subcortical regions [59-62], a variety of cognitive problems and interactions can be expected under the influence of (frontal) epileptic discharges [10,34,35]. The subtle working memory deficits we detected, could therefore origin from, or interact with other cognitive problems and might not be an isolated deficit.
Overall, with scores at the lower end of the normal distribution, the current study finds that working memory is relatively intact in primary-school aged children with FLE, as far as the objective cognitive tests are concerned. In contrast with these performance based measurement, teacher and parents ratings showed that 40 to 50 percent of the participating sample scored at least 1SD above average, and a third scored above the clinical criteria of the working memory scale of the BRIEF. Although the precise seizure frequency in our group is unknown and there is lack of imaging, we do know that all participants in our sample have frontal disturbances as confirmed by EEG registration. As mentioned earlier, there is evidence that working memory processes are related to the prefrontal areas [e.g. 32] and that FLE can lead to structural and functional disorders [e.g. 10]. Therefore, it might be safe to conclude that the working memory deficits in daily life in our participants can be, at least for some part, linked to their frontal lobe epilepsy. The unique availability of both parent and teacher ratings improves the reliability of this association.
In general, BRIEF scores in many clinical populations, rarely correlate with

cognitive tests [41,54]. The present study also reports few associations between performance-based measures and the BRIEF, confirming the outcome of other studies in epilepsy [44,53,63]. The strongest associations are found with the teachers' reports; this has not previously been studied in this population. Explanations for this inconsistency often mentioned in the literature are the lack of ecological validity for neuropsychological tests, the problems with computerised testing [64] and the response bias of teachers and parents [63,65]. Reported everyday behavioral and tested measures appear to tap different elements of executive functioning, however, confirming that the BRIEF reflects more daily "real-life" behavior, while performance in neuropsychological tests primarily predicts behavior in a controlled assessment setting [41,42,44]. Our results suggest that teachers report slightly more problems than parents. Another study in the same population confirms this tendency using the whole BRIEF [45] and strengthens the theory that executive function demands vary across settings.

Although the explanations about the limited associations discussed above sound valid and plausible, it is worthwhile considering an alternative explanation in (frontal lobe) epilepsy: working memory and attention are closely related [66,67] and teachers and parents could confuse the domains while rating. Another possibility is that teacher and parent ratings are based on observing children with epilepsy showing huge variations in their behavior and cognitive skills (e.g. impaired attention) due to the epileptic activity itself [23,53,68-70], to epilepsy as a stressor thus releasing Dopamine [71,72] and to fluctuating sleep quality, a main characteristic in our target group [73,74]. The impact of parental stress and reporting bias [65], as well as the use of anti-epileptic medication [75,76] on the results remain unknown, but may also contribute. Correlating subjective opinions based on variations in behavior and cognitive capacity with performance based measures such as neuropsychological assessment in children with FLE, is difficult and calls for systematic future studies on this issue.

There are several limitations to this study to acknowledge. The group as a whole is very heterogeneous in terms of epilepsy variables and overall neuropsychological deficits. In addition, the sample size is smaller than that necessary to show significant differences, according to the power analysis we conducted (38 participants). This was however based on determining a difference (of 2 SD) between an epilepsy group and ADHD group (with 80% power, two-sided alpha of 0.05). Unfortunately there were no children with only ADHD enrolled in the study. Furthermore, there is a normative reference group, but this group lacks age-appropriate data, which reduces the reliability of our data. Expanding the clinical group and adding a control group and possibly another clinical group would increase the power of the study. Expanding age groups to investigate possible delayed development is also necessary. Moreover, there might be a selection bias due to our setting. All children were referred for neuropsychological examination by the pediatric neurologist. The results can therefore not be fully generalized to a broader epilepsy sample.

Conclusions

Working memory in children with FLE is minimally affected compared to a normative reference sample, as assessed with performance-based measures. Parents and teachers, however, find working memory deficits in daily life behavior. Therefore, FLE can be associated with working memory problems on a daily life level rated by both parents and teachers. Future research is needed to differentiate further between daily life behavior and clinical behavior in children with FLE.

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CHAPTER 6

Cognitive control deficits in pediatric frontal lobe epilepsy

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Abstract

Executive dysfunction and behavioral problems are common in children with epilepsy. Inhibition and shifting, both aspects of cognitive control, seem related to behavior problems and are thought to be driven mainly by the frontal lobes. We investigated if inhibition and shifting deficits are present in children with frontal lobe epilepsy (FLE). Secondly, we studied the relationship between these deficits and behavior problems. Thirtyone children were administered the Stroop ColorWord Test and a digital version of the Wisconsin Card Sorting

Test (WCST). Parents completed the Behavioral Rating Inventory for Executive Function (BRIEF) and the Achenbach scale (Child Behavior Checklist (CBCL)). About 20% of the children displayed significant low results on the Stroop Effect. About 60% showed shifting problems on the WCST. Parents reported cognitive control and behavioral deficits in about a third of the children. Also, behavioral problems and deficits in inhibition and shifting in daily life (BRIEF) seem to be related. There were no correlations between questionnaires and the

Stroop and the WCST. Only in the group of children with many perseverative errors there were especially high correlations between Inhibit of the BRIEF.

Introduction

Executive function (EF) deficits in children with epilepsy have been frequently reported by parents on for example the Behavioral Rating Inventory for Executive Function (BRIEF) [1-4]. These deficits have also been demonstrated using validated neuropsychological tasks [5-8]. Although these studies strengthen the EF hypothesis, the EF domain remains very broadly defined comprising various functions. This makes effective assessment of EF difficult. As executive dysfunction seems to be a major contributor to poor quality of life in children with epilepsy [9], proper identification of this is critical to provide appropriate support and interventions [1,10,11]. Therefore, the aim of the present study is to pinpoint more precisely the assumed EF deficit by investigating an important element of EF: cognitive control.

Cognitive control refers to the higher-level processes that regulate lower-level processes needed to remain goal-directed, especially in the face of distraction [12]. The cognitive control model comprises three well-established subcomponent processes: shifting, updating and inhibition [13, 14]. Updating is defined as the ability to maintain and actively manipulate the contents of working memory. We do not investigate 'updating' in this study because this has already been investigated in a separate study on the same sample [15]. Results of this study imply that updating seems relatively intact in children with FLE. Also, updating is suggested to have a distinct role in the ,"cognitive control," model [16]. Furthermore, 'Inhibit' and 'Shift' are both part of the Behavioral Regulation Index (BRI) of the BRIEF [17-19], whereas 'Working memory' is a subscale of the Metacognition Index of the BRIEF, suggesting different cognitive control functions. The present study therefore focuses on the other elements of cognitive control: shifting and inhibiting.

The first component, shifting, involves moving between multiple tasks, operations, or mental sets and is positively correlated with intelligence [20]. It is closely related to cognitive flexibility [21], broadly defined as the ability to flexibly adjust behavior to the demands of a changing environment [22]. The second component, inhibiting, is the ability to deliberately lower the interference of unwanted stimuli or responses.

In general, deficits of these cognitive control processes may lead to weak attentional switching [21, 23], poor sustained attention [23], impulsive behavior [24] and behavioral problems [11]. From a neurological perspective, a complex circuit is involved in the number of different processes necessary for successful response inhibition and shifting, both in real life and in the laboratory. The neuroanatomical basis has been suggested to be in different cortical and subcortical regions, specifically in the prefrontal cortex [21,22,24]. Consequently, frontal lobe dysfunction and thus children with frontal lobe epilepsy, could be at risk of developing cognitive control deficits. Therefore, the present study aims

firstly to investigate whether these deficits are associated with pediatric FLE and hopes to elaborate on a number of recent studies on this subject [5,15,25].
We used two common EF tests to asses cognitive control in a clinical setting: the Wisconsin Card Sorting Test (WCST) assessing shifting and cognitive flexibility, and the Stroop Color Word Test (Stroop Test) assessing the inhibition of cognitive interference expressed as the 'Stroop Effect' [26]. Only few reports on the use of these tests in pediatric frontal lobe epilepsy are available. With regard to the WCST, results are inconclusive [27]: Some prior studies show reduced WCST performance, also in comparison to children with temporal lobe epilepsy [28]. In contrast there are also investigations concluding that the WCST is relatively insensitive to EF in children with epilepsy [27,29] or that WCST performance is reduced on a specific item [30]. For the Stroop Test, prior research in pediatric epilepsy shows that epileptic activity negatively affects performance on the Stroop Test [31,32].
Because cognitive control deficits are linked to externalizing and internalizing behavioral problems [1,11,15] the second aim of the study is to link scores of EF tests with questionnaires measuring problem behavior with the Achenbach Scales [33–35] and EF in daily life as displayed by the BRIEF
Based on the existing literature on patients with frontal lobe dysfunction, we hypothesize that children with FLE will display deficits in inhibition and shifting as assessed with the WCST and the Stroop Test and reported by parents on the BRIEF. Secondly, we hypothesize that cognitive control dysfunction will be related to behavioral problems in our sample.

Design

Sample

Children with FLE were referred for a broad neuropsychological assessment by the pediatric neurologist at a tertiary center. All parents were asked to complete questionnaires about perceived behavioral problems and executive functioning, while their children were being tested. Assessment of EF with validated and normative tests is possible from the age of eight. Cognitive flexibility skills begin to develop in early childhood, with a sharp increase in abilities between 7 and 9 years of age. Cognitive flexibility and inhibition skills are largely mature around age of 10 [21,36]. Previous work [37] has also shown significantly poorer performance in children with FLE aged 8–12 years compared to children with other epileptic syndromes. Therefore, inclusion criteria were age between 8 and 12 and IQ > 70 or school achievement scores above C level (Dutch CITO) in math and language. Children who would become 8 in the next two months were also invited to participate. Exclusion criteria were health and/or psychiatric problems, which could influence the neuropsychological assessment, except for attention deficit and hyperactivity disorder (ADHD), which is common in children with epilepsy [38]. 31 Children met the inclusion criteria. All parents completed both questionnaires. Epilepsy diagnose was based on the International League Against Epilepsy criteria and confirmed by an EEG recording. The study was approved by the Ethical Committee of MST Enschede and parents gave their informed consent.

Measures

Wisconsin Card Sorting Test

The WCST (classification) of the computerized test battery FePsy [39] was used to assess set shifting and cognitive flexibility. It consists of 128 digital cards to categorize on the color of its symbols, the shape of the symbols, or the number of the shapes on each card. The only feedback is whether the classification is correct or not. Outcome is the quantity of categories (with a maximum of 6), total errors and perseverative errors. Unfortunately, no clinical cut-offs are available for the number of categories and amount of errors. More than 16 perseverative errors are considered as significantly elevated.

The Stroop Color Word Test

The Stroop Color Word Test, Dutch version, [40] was used to assess inhibition. Subjects are required to read three different cards as fast as possible. Two of them represent the ,“congruous condition,“ in which subjects are required to read names of colors printed in black and name different color patches. In the third table color-words are printed in an inconsistent color ink (for instance the word ,“green,“ is printed in red ink). Thus, in this ,“incongruent condition,“, patients are required to name the color of the ink instead of reading the word. In other words, the patient is required to perform a less automated task (naming ink color) while inhibiting the interference arising from a more automated task (reading the word). This difficulty in inhibiting the more automated process is called the Stroop effect [41]. Working pace is measured in seconds and than computed into a normative score. A score of decil 1 (low) and 10 (high) is considered statistically significant for all cards.

The BRIEF and CBCL

Parents completed the Child Behavior Checklist (CBCL) and the Behavioral Rating Inventory of Executive Function (BRIEF). This analysis focuses on the externalizing and internalizing scale of the CBCL and the two subscales Shift and Inhibit and the Behavioral Regulation Index (BRI) of the BRIEF to assess more daily life behavior. The BRIEF has good psychometric properties that include appropriate construct validity. Internal consistency is strong and the test-retest reliability is also high [42]. A score 1.5 SD (≥ percentile 93) above average is considered statistically significant for the indices.

The CBCL is a well-established behavioral questionnaire with good psychometric properties [35], also for children with epilepsy [34]. A score 1.33 SD (≥ percentile 90) above average is considered statistically significant for the main scales.

Statistical analysis

Data were analysed using the Statistical Package for Social Sciences (IBM SPSS Statistics 23.0). The data, corrected for age, were compared with normative data of the Dutch population. For the digital WCST we did not use normative data because those were not available. In the analysis we compared scores according to age. To explore group differences based on perseverative errors and Stroop effect, we categorized into few (< 16 errors) vs many (≥ 16 errors) perseverative errors and Stroop effect (< decil 1) vs no Stroop effect (≥ decil 2).

Differences in normally distributed scores between the FLE cohort and the reference values were tested with one-sample t-tests or, in not normally distributed data, with nonparametric tests. The association between the tests and the questionnaires was investigated. As sample sizes are relatively small, effect sizes are shown when appropriate using Cohen's *d*.

Results

Patients' demographic characteristics are presented in table 1.

Table 1. Demographic and epilepsy variables

Characteristics	Value
N	
1. Children	31
2. Parents	31
Participants	
1. Gender (male:female)	18:13
2. Mean age (±SD) in years at assessment	9.2 ±1.6
Age at seizure onset	
3. Mean age (±SD)	4.6 ± 2.8 years
Duration of epilepsy	
1. Mean duration (±SD)	4.6 ± 2.7 years

Figure 1 shows the results of the Stroop Test. Working pace on card 1 (reading words) is significant low (decil 1) in a third (n=10) of the sample and slowest of all three cards. Sixteen percent (n=5) scored significantly lower on the 'Stroop effect' compared to the normative sample.

In figure 2 results of WCST are displayed controlling for age. It shows that task performance was not related to age: mean errors, mean perseverative errors and the number of categories remained stable with age. More than 60 percent of the children scored in the clinical range (≥ 16 errors) for perseverative errors.

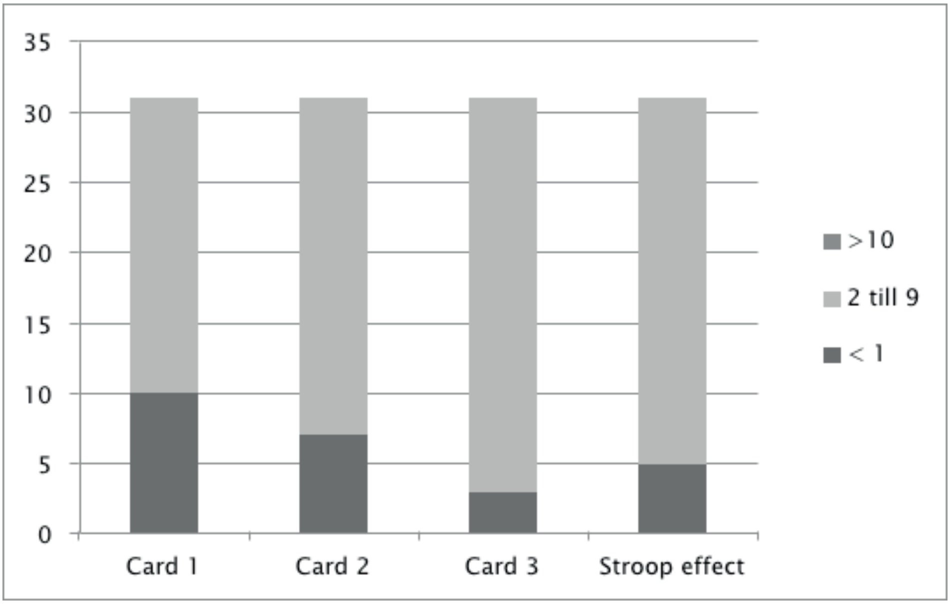
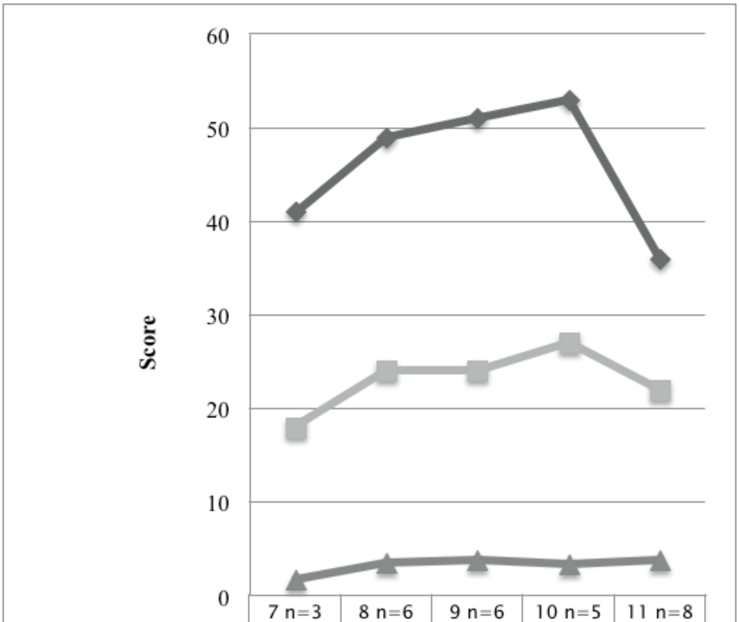


Figure 1: Frequencies scores Stroop Test



	7 n=3	8 n=6	9 n=6	10 n=5	11 n=8
Mean errors	41	49	51	53	36
Mean perseverations	18	24	24	27	22
Categories	1,7	3,5	3,8	3,4	3,8

Figure 2: Scores WCST
Note: Scores displayed per age

About a third of the parents reported behavioral and cognitive control (inhibit and shift) problems on the CBCL and the BRIEF (figure 3).
Except for one scale, correlations between the CBCL and the BRIEF questionnaires were moderate (table 2), indicating that cognitive control (shifting and inhibiting) in daily life is associated with behavior as reported by parents.
In contrast, the parent proxy reports did not correlate with the neuropsychological performance (the Stroop Test and the WCST) (table 3) in the total group. However, especially in the group with many perseverative errors (on the WCST) these correlations were moderate between the Inhibit of the BRIEF and the Stroop Test.
The mean scores between age groups on the CBCL appeared to show huge variations and we therefore conducted post hoc comparisons. This indicated that the mean score for internalizing problems of children aged 10 to 12 (M=82.00, SD=18.59) was significantly different (p = .02) than the mean score of children aged 8 to 10 (M=58.94, SD=31.80). There was no significant difference on externalizing problems between the 'older' children (M=70.43, SD=30.68) and 'younger' children (M=65.71, SD=26.03).

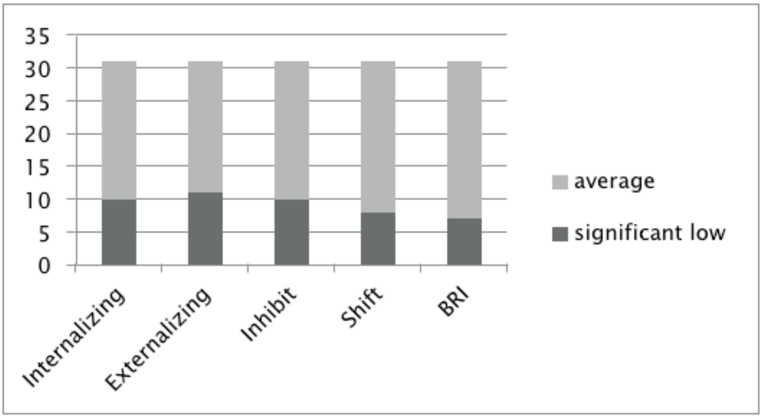


Figure 3: Frequencies scores questionnaires

Table 2: Correlation between the questionnaires

BRIEF \ CBCL	Internalizing	Externalizing
Inhibit	.34	.62***
Shift	.65***	.41*
BRI	.60***	.64***

Correlations are shown using Spearmans r_s
* $p \leq 05$
*** $p < .00$

Discussion

This study focused on two aspects of cognitive control, namely inhibiting and shifting in children with FLE. Impaired response inhibition, as measured by the Stroop Test, was found in about 20% of the participants when the conservative cut off level was used (-2SD). Performance on the Stroop Test (or the almost similar Color-Word Interference Test of the D-Kefs) has hardly been investigated in children with (frontal lobe) epilepsy. Nevertheless, our data seems to replicate the findings of a limited number of studies [43-45]. Furthermore, our data are consistent with several studies suggesting that people with frontal lobe dysfunction are impaired to some extent on different tasks of inhibition [45-47]. Furthermore, children displayed slowness on the Stroop Test, which was most pronounced on card 1 of the Stroop Test, but was also present on card 2. Psychomotor speed problems and general slowness are often reported in children with epilepsy [48,49]. It could therefore be argued that poor performance on the Stroop Test in our sample might be related to an attention problem and/or a problem in (processing) speed rather then a specific impairment in response inhibition [43,44].

For the WCST, the large amount of perseverative errors in 60% of the participants indicates weak shifting, which concurs with other studies [28,37,44]. Age factor was not associated with shifting abilities, which is in contrast with many developmental studies, showing that EF skills normally improve with age and brain maturation [21,50]. An explanation for this could be that in our group with frontal disturbances, the development of shifting skills levels off with age, whereby executive dysfunction emerges over time [50,51].resulting in long-term developmental ,"lagging behind,".

In concordance with the results on test assessment, parents reports on the BRIEF show inhibit and shifting deficits in about a third of the sample. Parents also reported behavioral problems to the same extent. These reported cognitive control deficits on the BRIEF seem to be related to the reported behavioral problems on the CBCL. This concurs with other studies [1,11,25,37], suggesting that having cognitive control deficits places a child at risk for developing behavioral problems.

6

Table 3: Correlating questionnaires and Stroop/WCST

Total group (n=30)	Inhibit	Shift	BRI	Int	Ext
Interference	.26	.13	.15	.06	.10
Card 1	.40*	.25	.30	.04	.14
Card 2	.35	.27	.31	.01	.09
Card 3	.34	.29	.26	.02	.17
Total categories	.21	.17	.19	.03	.07
Total perseverative errors	.31	.04	.20	.03	.23
Total errors	.08	.06	.00	.21	.22

Few perseverative errors (n=11)	Inhibit	Shift	BRI	Int	Ext
Interference	.02	.19	.23	.04	.11
Card 1	.11	.36	.27	.40	.05
Card 2	.44	.63*	.52	.52	.28
Card 3	.25	.66*	.48	.29	.05
Total categories	.60	.51	.62*	.36	.46
Total perseverative errors	.02	.06	.16	.40	.46
Total errors	.36	.36	.65*	.47	.36

Many perseverative erros (n=19)	Inhibit	Shift	BRI	Int	Ext
Interference	.54*	.21	.29	.06	.08
Card 1	.56*	.17	.33	.15	.04
Card 2	.47*	.12	.32	.13	.18
Card 3	.54*	.20	.31	.04	.14
Total categories	.12	.11	.12	.11	.14
Total perseverative errors	.19	.04	.08	.24	.22
Total errors	.12	.02	.10	.19	.09

Correlations are shown using Spearmans r_s
* *p*≤05

However, significant connections between our neuropsychological measurements and the questionnaires including the BRIEF are low. This finding replicates the results in this sample on working memory [15] and previous findings [27,52,53]. When considering children with shifting problems only, we did found associations between Inhibit of the BRIEF and the Stroop Test. The sample size is small, but this might indicate that children with poor shifting skills also show other executive dysfunction.

Post hoc analysis yielded that parents of the children aged 10 to 12 reported far more internalizing problems compared to children age 8 to 10. As longer duration of epilepsy is considered to be a risk factor for psychopathology [54-57], this could be expected. We could, however, not confirm this same finding for externalizing problems; these problems were reported to the same extent in both age groups. The perceptibility of mood and anxiety problems (so called internalizing problems) is low in young children [58], which might indicate that these problems are underreported. Therefore, it might be worthwhile to take unreliable proxy report into consideration when interpreting results [59,60].

The study has several limitations. Firstly, it is not controlled. Comparison to normative data gives information for clinical use, but a larger group (clinical and non-clinical) enables further comparisons, for example based upon epilepsy subgroups. Epilepsy variables can be taken into account in identifying people who are particularly at risk for developing cognitive deficits and behavioral problems. Secondly, due to setting, there is a selection bias as children were referred by a pediatric neurologist. The results can therefore not be fully generalized to a broader epilepsy sample. Thirdly, inhibiting and shifting components of cognitive control are separable but also correlated [14]. Thus, indexing these abilities solely with experimental tasks and manipulations is unlikely [16]. Reported everyday behavioral and tested measures do appear to tap different elements of executive functioning, confirming that the BRIEF reflects more daily ,"real-life," behavior, while performance on neuropsychological primarily predicts behavior in a controlled assessment setting [7,42,53]. Lastly, the sensitivity of the WCST has been questioned in pediatric epilepsy [27,29] and we even used a different, digital, version, which is not investigated much in children with epilepsy. Unfortunately there are not many validated alternatives to investigate these specific functions.

The WCST might not be fully reliable and we failed to find many deficits on the Stroop Test. However, there is also evidence for inconsistencies in parental reports for several reasons [60], which makes it for future research necessary to rely on both informant- and performance based measures.

Conclusions

Inhibition and shifting deficits are found with performance-based measures in children with FLE. These are also frequently reported by parents on daily life level, to the same extent as behavioral problems. Cognitive control in daily life and behavior seem related, whereas performance based measures of cognitive control and behavior seem less related. Shifting problems might indicate the presence of other executive dysfunction.

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CHAPTER 7

General summary & Discussion

Epilepsy is a chronic neurological disease, often characterized by many seizures. On top of this, children with frontal lobe epilepsy (FLE) may have behavioral and learning problems, which can place a heavy burden on both patient and caregivers. Epilepsy does not only affect quality of life of these children directly, but it also limits the development of cognitive and socio-emotional skills. One of the afflicted skills might be the executive functions (EF). Although there is growing knowledge of the underlying neuroanatomy, there is still unclarity about specific neurocognitive deficits and their impact on daily functioning of this patient group. In addition, clarity is needed to translate the knowledge into behavioral interventions

The main aim of the present thesis is to gain more insight into the association between FLE, neurocognitive problems and behavioral issues in school aged children with FLE. The thesis addresses different aspects of EF and its consequences when EF deficits occur. In the final chapter, the main conclusions will be summarized and discussed on the basis of the eight initially formulated objectives in the introduction chapter.

Part I: Behavior

Part I starts with a review of the literature on behavioral and socioemotional problems associated with EF deficits in children with epilepsy in general. The following chapters build on the conclusions of this review. The first part focusses on behavioral problems indexed by the Child Behavior Checklist (CBCL for parents) and the Teacher Report Form (TRF for teachers) in concordance with the Behavior Rating Inventory of Executive Function (BRIEF). The burden of parents of children with FLE is investigated with the Nijmeegse Vragenlijst voor de Opvoedingsituatie (NVOS).

Objective 1: Systematically review the empirical literature on the association between executive dysfunction and behavioral and socioemotional problems in children with epilepsy (chapter 2).

This systematic literature review was conducted in the year 2018 and expended in 2020, in compliance with the guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [1]. Various search terms were used to cover all research on EF in relation to behavior in children with epilepsy. After an extensive literature-search, 26 empirical studies were identified.

Results indicate much diversity among the studies with respect to tests, questionnaires and cut-off points. Also, the heterogeneity of research groups was high with different epilepsy types, seizures and demographics, 16 studies out of 26 reported a positive relationship between a wide range of EF problems and behavioral disturbances. 10 studies reported that low neuropsychological functioning was accompanied by higher behavioral disturbances. A surprising

result was that social dysfunction seemed to be associated with poor (working) memory.
Epilepsy variables most associated with different behavioral disturbances and/or cognitive deficits were early age at onset and high seizure frequency. Differences between focal epilepsies were hardly reported.
Although the results of this review were not conclusive for specific EF and epilepsy variables, findings did seem to point towards a positive relationship between executive dysfunction and behavioral disturbances, more specifically, lack of cognitive control was linked with behavioral regulation problems. Attention problems were most frequently reported, which is not surprising given that the rate of comorbid ADHD in epilepsy is high [2].

Objective 2: Investigate which behavioral problems are most experienced by parents and teachers of children with frontal lobe epilepsy (chapter 3).
32 Parents and teachers of children with FLE were recruited in a tertiary epilepsy center in the Netherlands. They completed questionnaires about the children concerning behavior (CBCL, TRF). 35% of the children were rated in the abnormal range on the CBCL by parents, whilst more than half of the children had more than average internalizing as well as externalizing behavioral problems. Attention problems were reported up to 44%. Teacher reports were slightly different. They experienced abnormal behavior in 25% of the children. Internalizing behavioral problems were experienced in about 40% of the children and externalizing behavioral problems in about 30%. Although teachers also reported attention problems in about 40%, there was a difference in contrast to parents' reports; teachers mainly reported attention problems as 'more than average' compared to other children, whereas parents reported it as deviant. In the social domain, teachers reported more social problems than parents (40% vs. 25%), whilst parents reported more thought problems compared to teachers (40% vs. 25%).
The findings are consistent with other studies using the CBCL/TRF in children with epilepsy, which might suggest that children with FLE do not differ on behavioral functioning compared to children with other epilepsies. Surprisingly, children with FLE were rated as having fewer mood and anxiety problems than, as extensively reported in the literature, children with other epilepsies. Epilepsy variables hardly contributed to the results, however there was a small trend seen for more problems in children with left FLE.

Objective 3: Investigate the relationship between executive functions (EF) and behavior in school and at home as reported by teachers and parents of children with frontal lobe epilepsy (FLE) (chapter 3).
At time of publication this was the first study which compared parents' and teachers' reports of the BRIEF and CBCL/TRF in children with epilepsy. Correlations between parents and teachers reports about behavior were almost all moderate

to high. This is also true for the reports about EF between both responders. This indicates that children with FLE display a variety of behavioral problems, which seems stable across different settings. The unique availability of both reports strengthens these results.

Furthermore, moderate to high associations between executive and behavioral functioning confirmed a strong association between the two. This relation was most pronounced in the teacher ratings. In the teacher reports, metacognitive functioning highly correlated with externalizing behavior. Specifically attention problems and aggressive behavior were highly associated. In the parent reports, especially behavioral regulation on the BRIEF was related to behavioral disturbances in general. Furthermore, attention (CBCL) and working memory (BRIEF) were highly associated. This confirms findings in other studies on attention and working memory, in which the interplay between the two, but also shared constructs is suggested [3,4]. The difference in EF demands across settings might explain differences in the two reports; parents reported relatively many behavioral regulation problems, whereas teachers reported relatively more metacognitive problems. Overall, attention problems were linked to the whole range of EF.

Objective 4: Explore parental burden of parents of children with frontal lobe epilepsy (chapter 4).

Epilepsy can affect childs' behavior but also their parents possibly leading to parenting stress and burden. This, in turn, may affect the child's behavior in different ways. Especially, externalizing behavioral problems seem to place a great burden on parenting. In addition, the literature suggests that behavior as well as parenting might interact with epilepsy factors. For instance, comorbidity as well as epilepsy variables can exacerbate problems. Conversely, seizures can be induced by stress in which disturbed parent-child interaction can play a role. In view of this, chapter 4 investigates the burden of 31 parents of children with FLE using the NVOS.

It appeared that only parents whose children have had epilepsy for more than 5 years experienced elevated burden. These parents also felt that they were less able to manage parenting and experienced an inadequate interaction with their child. Parents of children who had had epilepsy for less than 5 years reported average burden. It is concluded that enduring epilepsy could therefore be a risk factor in developing parental burden.

Correlation between NVOS and externalizing behavioral problems was high. Regression analyses showed that experiencing that the child is a burden predicted scores for externalizing behavioral and behavioral regulation problems. Furthermore, more outgoing behavior predicted scores for experienced burden. These findings seem to strengthen the suggested bidirectional effect between parental burden and perceived behavioral problems. Arrived at this point, it must be underlined that almost none of the parents was excessively negative about

their child.
A remarkable coincidental finding in this study was the unreliability of parent reports. Although it is known that parents' reports can be inaccurate [5], in the current sample up to 50% of the reports seem to be inconsistent.

Part II: Cognition

The focus in part II, is on cognitive control, associated with the prefrontal area subserving the EF that is associated the most with behavior deficits in frontal lobe epilepsy. Cognitive control refers to the higher-level processes that regulate lower-level processes needed to remain goal-directed, especially in the face of distraction. It comprises of three subcomponents: shifting, updating and inhibition. These neurocognitive components can be described as elements of 'cool' EF, in which reasoning plays an important role.
In part two of the thesis this was assessed using different working memory tasks for updating, the Wisconsin Card Sorting Test (WCST) for shifting and the Stroop Color Word Test (SCWT) for inhibition. Furthermore, the subscales 'working memory', 'inhibit' and 'shift' of the Behavioral Rating Inventory for Executive Function (BRIEF) were used to obtain information about cognitive control in daily life (chapter 3,5,6).
In the two studies, it becomes clear that children with FLE show 'cool' EF problems. They perform worse than healthy peers on tasks that assess inhibition and shifting (chapter 6), but overall their performance is comparable to the control group on tasks that assess working memory (chapter 5). Parents as well as teachers report many EF problems in daily life (chapter 3,5,6).

Objective 5: Asses if parents and teachers of children with frontal lobe epilepsy report executive function problems in daily life (chapter 3,5,6).
In chapter 3, EF problems in daily life were investigated using the BRIEF parent and teacher version. Parents as well as teachers reported abnormal general executive functioning in daily life in 20% of the children and 'more than average' problems in 40% of the children. Behavioral regulation problems, which includes emotional control and abilities to shift and inhibit, were reported frequently: teachers reported these problems up to 60% and parents up to 40%. This means that the rated ability to shift cognitive set and modulate emotions and behavior via appropriate inhibitory control is affected in the children with FLE across different settings.
Metacognitive problems were reported to a somewhat lesser extent compared to behavioral regulation problems. Teachers reported up to 40% in general and experienced especially working memory (50%) and monitor problems (40%). About 30% of the parents reported metacognitive problems and also experienced in particular working memory (40%) and monitor problems (40%). On the whole, differences in both reports are probably explained by different executive function

demands across settings.

Objective 6: Explore the association between reported and tested executive functioning of children with frontal lobe epilepsy (chapter 5,6)

In general, performance in neuropsychological tests primarily predicts behavior in a controlled assessment setting, but cognitive and behavioral measures rarely correlate [6]. From this perspective it was not surprising that correlations between the BRIEF and tested EF are low [7]. Only few studies have addressed the relationship between tested and reported EF in children with epilepsy. As was described by Hessen, Alfstad, Torgersen & Lossius [8], inconsistent findings between studies therefore calls for further investigation. The WCST and SCWT, as well as the various working memory tasks we used were not systematically studied concerning this association in children with FLE.

Our results show that there was no significant correlation between the SCWT and the BRIEF. Also for the WCST this association was missing. However, when considering children with only shifting problems, we did found a moderate association between Inhibit of the BRIEF and the SCWT. For working memory there were only small associations found, especially for teachers' reports.

Objective 7: Investigate if children with frontal lobe epilepsy have poorer working memory skills than normal controls (chapter 5).

Adequate functioning working memory is of great importance in daily life. In children with FLE, working memory abilities seem reduced as reported by parents and teachers (chapter 3) and there are several reasons why working memory can be compromised in FLE. In chapter 5, working memory was investigated using performance-based measures carried out in children with FLE. In general, auditory working memory has most frequently been investigated, while research on visual working memory is sparse. Therefore, working memory was investigated with different tests to cover all domains.

As assessed with these tests, there was no significant difference between children with FLE and the normative group on several tasks for working memory, which was also reflected in the recent study of van Iterson & de Jong [9]. However, performance on recognizing figures, which were offered simultaneously, was significantly poorer in the patient group. This was independent of epilepsy variables such as seizure focus. Furthermore, it appeared that the growth of working memory skills flattens with age, suggesting possible delayed development of working memory in the long term.

Objective 8: Determine if children with frontal lobe epilepsy show deficits in inhibition and shifting (chapter 6).

Cognitive control problems seem to occur often in children with FLE as reported

by parents and teachers. In chapter 6, results on cognitive control (inhibition and shifting) using performance-based measures (SCWT and WCST) In comparison to a healthy normative group, more than half of the sample made far more perseverative errors on the WCST, which is an indication of weak shifting skills. Strikingly, mean 'raw' scores did not improve with age, possibly suggesting a reduced development across age of shifting skills. For the Stroop, only 20% of the sample performed significantly worse compared to normative controls, indicating that inhibition skills might be moderately affected in the children. An additional finding in this study was response slowness in the patient group, which might indicate an underlying attention problem, and/or general mental slowness rather than an impairment in response inhibition.
An important recommendation, which might give direction for future studies and interventions, is to consider the results based on shifting deficits. It appeared that specifically the group children with shifting deficits showed high associations between inhibition on test assessment and inhibition as reported by parents. This could indicate that poor shifting skills put a child at risk for developing other EF problems.

General discussion

This present thesis describes the results of studies on behavior and executive functioning, specifically cognitive control, in children with frontal lobe epilepsy. The main aim was to gain more insight into the association between FLE in school-aged children, neurocognitive problems and behavioral issues.

Frontal lobe (epilepsy)

The first well-described case with frontal lobe damage, Phineas Gage, led to the understanding that damage to these areas has implications for cognitive and behavioral functioning [10]. Although not all children in the studies in this thesis suffer from frontal lobe damage, as confirmed by imaging, EEG recording confirms frontal lobe dysfunctioning in all of these children. As such, it can be argued that reduced neurological functioning shows overlap with problems as seen in patients with traumatic brain injury in the frontal area. In addition, a proportion of the children in this study have frequently seizures causing the already affected brain to be affected even more. The frontal lobes are quite consistently linked to the EF [6, 11-13] and there is emerging evidence that these EF in turn are related to behavioral disturbances [11, 12, 14]. This combination of symptoms is sometimes referred to as the ,"frontal syndrome," [15, 16].
This ''one to one'' relationship between brain injuries and functioning in daily life might be apparent from a localizationist view of brain functioning. But the terms relating to frontal functioning can also be ciritizized. Recent studies propose switching to the concepts of cerebral connectivity and plasticity – i.e., a brain organization based on dynamic interrelationships between parallel distributed

networks [16, 17]. Although the prefrontal cortex (PFC) undoubtedly still plays a major role in EF across development, the PFC has to be considered within the context of a constant interplay with other key nodes in the network [17]. Moreover, recent studies in epilepsy also begin to consider epilepsy as a network disease [18-20]. Besides, there is evidence of specific 'frontal' neuropsychological deficits in other epilepsies [9, 21]. Furthermore, prefrontal metabolic asymmetries in temporal lobe epilepsy might play a pivotal role [22]. Alternatively, neurocognitive problems might be related to a genetic factor; that is to say, relatives of patients with epilepsy show parallel profiles of cognitive abilities with significant deficits on neuropsychological assessment, including working memory [23, 24] but with a milder symptomatology compared to patients [23]. From this perspective, studying specific focal epilepsy groups, like in this thesis, would be rather meaningless. Nevertheless, in our specific sample of children with FLE it is clinically evident that behavior can become greatly disturbed, which is not frequently observed in other epilepsy groups, but has been reported in patients with traumatic brain injury in the frontal area (e.g. 14). Being part of a network disease might therefore not necessarily mean that there cannot be specific functional loss, which can lead to adjoining behavioral disturbances.

We were unable to identify specific epilepsy variables as confounders in the relation between cognitive deficits and behavioral problems. This means that it remains unclear which children with FLE might be more vulnerable for delayed cognitive and socioemotional development. However, early age at onset and longer duration of epilepsy might be qualified as risk factors in developing cognitive and behavioral problems. This confirms results from other studies [25-28], also specifically for frontal lobe epilepsy [29].

Whilst advances in structural neuroimaging have enabled a deeper understanding of the contribution to improvements in EF of changes in cortical thickness, volume, and white matter in the PFC and connected areas, future research is needed to identify specific neural substrates of the EF [17].

Although neurological impairment is related to cognitive and behavioral problems, in our patient group poor quality of sleep also has to be taken into account. FLE is often characterized by nightly seizures and therefore poor nights. Studies show that already one poor night sleep shows a striking reduction of cognitive performance [30, 31]. Thus, in our specific group, continuous poor sleep might be of negative influence on cognitive functioning. Unfortunately, data of sleep quality in the current sample is lacking. From a clinical perspective it can be cautiously suggested that children show less behavioral problems after adequate epilepsy treatment and as a result less to no nightly seizures. Nevertheless, children with adequate seizure control still exhibited EF and behavioral problems. This suggests that (frontal) seizures are not solely the cause of these difficulties, but might co-exist with EF deficits as a symptom of the underlying epileptogenic condition [26].

Executive function

Executive function is an umbrella term comprising very different cognitive processes and behavioral competencies to engage in independent, purposive, goal-directed and self-serving behavior [32]. To assess these functions, a wide range of tests, inventories, and tasks have been developed, under the same umbrella term, in countries with different cultures, developmental levels, and different languages, and also normed in unlike settings [33]. It is therefore not surprising that different studies often do not find (similar) associations between medical and psychological conditions. Furthermore, these very diverse findings based on measures that all are named as executive measures raises the question whether the term EF may be too broad to be meaningful in many research and clinical settings. That's why the current thesis tried to unravel the executive functions using the concept of cognitive control, which is clearly described in the literature and seems mostly related to behavior [17,34].

This thesis revealed that children with FLE show cognitive control deficits (chapter 3 & 6), as well as assed with performance-based measures as obtained with proxy measures of parents and teachers. A very important finding in test assessment was that the specific EF was not only developed slower than the norm but also flattened with age (chapter 5 & 6), which means that over time, performance worsened compared to the norm, the so-called 'growing into deficit'. Kanemura [35] highlighted that seizures from the frontal areas are associated with disturbance of prefrontal brain growth over time and this lasted beyond seizure remission. Furthermore, Bell & Wolfe [36] argued that in children with epilepsy, early impairment might affect reorganization in the brain. The cognitive delay in children with FLE might therefore be seen as a consequence of the long-term changes in brain development. As such, this study contributes to the existing literature about 'growing into deficit' but specifically for children with FLE. This finding for FLE specifically replicates findings of others [18,37].

In line with earlier work, this thesis could not confirm working memory problems with test assessment in our patient group with FLE. Emerging evidence shows that working memory is not completely localized in the prefrontal cortex: the frontal and parietal cortices have been identified as core neural substrates of WM from infancy onwards, and subcortical structures have also been shown to be involved. Additionally, the connectivity between frontal and parietal cortices, and the network they form, are also important in facilitating the development of WM [17].

When interpreting these cognitive results, it needs to be said that performance on the cognitive tasks, using traditional tasks, was comparatively better than scores on the proxy measures concerning daily life behavior. This discrepancy between 'laboratory' EF functions and proxy measures could be firstly related to ecological validity of the traditional tests, which seems especially true for the used working memory tasks. Particularly striking in the relatively good results on the working memory tasks is that we found a link between working memory and attention, which is in line with other investigations. As mentioned earlier, attention problems are very commonly reported in children with epilepsy. Since there is some kind of connection between attention and working memory, it is apparent that working memory problems cannot be confirmed with the performance based measures, which adds to the 'ecological validity hypotheses'. If working memory and attention can be distinguished from one another has been the subject of much research and theoretical discussion in the field. Overall, the evidence suggest important links between the development of at least some aspects of attention and working memory abilities during the early years, potentially leading to a convergence of processes that allow for the emergence of higher-order EF skills during the pre-school period [17].

Secondly, clinical observations of children with FLE also deviate from the performance based measures and confirm the proxy measures. Most cognitive tasks rely upon explicit mechanisms for understanding the task and for providing the response (each one having a single, intrinsic correct solution), while most of our actions in daily life are automatic or have little access to conscious monitoring [38]. Daily life evaluations are a complex interplay between context, properties of the situations, accumulated reward history based on positive and negative reinforcement, which estimates the outcome and value of an (social) action [39, 40]. In this thesis lowered performance and ratings concerning shifting was most remarkable (chapter 6). This means that children with FLE did indeed exhibit more trouble moving between multiple tasks, operations and mental sets. Furthermore, they show difficulty in flexibly adjust behavior to the demands of a changing environment. In addition, the children with most shifting difficulties have also less ability to deliberately lower the interference of unwanted stimuli or responses. Although we were unable to capture the completely limited functioning in daily life, it is evident that our thesis covers at least part of the EF problems as described by parents and clinically observed.

A third argument for the inconsistency between tested and repored EF concerns the inconsistency and, as a consequence, reduced validity of the proxy measures. This thesis revealed that a large proportion of the parents tended to be inconsistent in their ratings (chapter 4). This outcome is not entirely surprising as is it frequently described in the literature, caused by a variety of factors [5,41]. However, the results don't have to be totally discarded: The inter-rater reliability (parent and teacher) of the Behavior Rating Inventory of Executive Function (BRIEF) was high and in concordance with normally developing children [7], confirming the strength of parent as well as teacher ratings in this population. We did detect subtle differences between parent and teacher ratings on different subscales (chapter 3). These findings may reflect different EF expectations across settings, such as the increased demands for planning, organization and self-monitoring.

A not totally unexpected finding was the elevated ratings concerning attention.

Although most children were not diagnosed with Attention-Deficit Hyperactivity Disorder (ADHD), ratings of attention deficits are high across the two different settings. It is known that children with epilepsy are at risk for developing ADHD [2]. A leading theory on ADHD proposes core deficits in executive functioning abilities [42]. This might probably also reflects the elevated 'attention deficits' levels in children with FLE and raises the question whether children with FLE would benefit from this diagnose. Instead, disentangle the different EF components, as we did in this thesis, would give more insight in the underlying aetiology and the most appropriate intervention.

Behavior

In self-report as well as proxy report, prefrontal lesions are associated with social/emotional disturbances and diminished motivation [11,13-15]. Unfortunately, in this thesis, self-report wasn't possible because of the young age of the participants. Moreover, self-report in this specific group with frontal lobe dysfunction is hindered because there might be deficits in behavior self-awareness [13,15]. Therefore, we had to rely on proxy reports, knowing that, as previously discussed, these reports might be less reliable. In clinical observations it is apparent that these children with FLE suffer from (sometimes massive) behavioral regulation problems, resembling behavior of psychiatric patients. Independent of neurological problems, there is evidence that behavioral disinhibition in early childhood may be linked with later disruptive behavior and comorbid mood disorders in normally developing children [43]. This might imply that children with FLE are more at risk in developing abnormal behavior. Indeed, damage to the medial prefrontal and orbitofrontal cortex is related to personality changes, leading to psychiatric symptoms of e.g. autism or psychopathy [44,45], although not all symptoms always meet the criteria of DSM classifications [45,46]. In this thesis we confirm that parents as well as teachers indicate that children with FLE exhibit deviant behavior (chapter 3), resembling outcome of other studies in children with epilepsy. In contrast to what is normally reported, mood and anxiety problems could only be confirmed to lesser extent. In this study, epilepsy variables did not contribute to the results, making it unclear whether there is an association with any epilepsy variable like localization.

It is however apparent and unexpected that a proportion of the parents did not report behavioral issues. This may be explained by the fact that parents experience that children are doing well despite their epilepsy, a so-called response shift [47]. This means that items of questionnaires may not be age appropriate to the child's current environment [48]. Furthermore, as earlier mentioned, the child's functioning seems also related to seizure frequency, causing difficulty in rating the (changing) behavior. In conjunction with this, it was already clear that sleep deprivation impacts cognitive functioning, but recent studies suggest that it also has implications for self-regulation and social behavior, which includes behavioral and emotional regulation [49]. This means that behavior can differ by day and is also rated in this (inconsistent) manner. Alternatively, despite the fact that the behavioral questionnaires used in this thesis are valid and frequently used in patients with epilepsy, current questionnaires might be limited in capturing (subtle) behavioral differences in daily life, which are mostly expressed only in unstructured evironments as at home [50].

Especially more outgoing behavior (e.g. behavioral regulation issues) is generally associated with increased parental stress [51] and it appeared that this is also true for children with FLE (chapter 4). Caring for children with epilepsy and comorbid cognitive problems are known to place a burden on parents in general [52]. Even after years of seizure freedom, parenting stress, parents' well-being and family functioning still are affected [53,54]. Unexpectedly, a large proportion of the parents reported no elevated burden in caregiving. However, when the epilepsy endured for at least 5 years, this increased and it was also associated with more parenting problems and worsened caregiver-child interaction (chapter 4). This finding could indicate that duration of epilepsy is a risk factor in increasing parental stress. Results about the assocations between duration of epilepsy and parental stress are not yet conclusive [55,56]. As not all children had frequent seizures and/or comborbidity, this might imply that parental burden is not per se associated with only seizures and their comborbid cognitive disabilities. This might better be understood from the necessity of continual guardianship that parents have to provide to their child in order to warrant his or her safety, which changes their lives. They have to make many adjustments and the children keep lacking age-appropriate self-dependence in which they continuously require special support [53,56].

Strenghts & Limitations

The data in the present thesis were collected only in a tertiary epilepsy centre. This automatically raises the question whether the findings can be generalized to all children with FLE. Van Iterson [27] addresses this same issue with a fairly similar sample and concludes that it is generalizable, because our centre works nationwide and is largely equivalent with the other tertiary epilepsy centre. It needs to be said however, that there still remains methodological challenges concerning the sample in the current study. In the very beginning, the thesis was indented to compare children with FLE and children with ADHD. Unfortunately, collaborating with a health care institution in order to recruit children with a confirmed diagnose ADHD appeared to be a challenging task. Eventually, the recruited ADHD sample was too small to be meaningful in any way, so we needed to dismiss this. However, the initial sample size was calculated for the specific comparison between children with FLE and children with ADHD. With this said, it becomes clear that current sample size is relatively small for only one group.

Furthermore, although the whole sample consists of children with FLE, there is still much heterogeneity in terms of different other epilepsy variables. These differences make it difficult to identify disease-related variables that are associated with EF and behavior. Comparing these data with different epilepsy groups and expand the age groups would make it possible to analyze more in depth. Also, it can be worthwhile to study the group longitudinal to confirm whether the development curve levels off further. Moreover, with the lack of a control group the thesis also lacks age-appropriate data.

In the present thesis, the children with FLE were almost all clinically referred by the neurologist for whom concerns about cognitive and/or behavioral development had risen. The data may therefore be well generalizable to other children with complicated FLE, but to lesser extent to children with uncomplicated FLE. The co-occurrence of epilepsy and school-related difficulties [57-59] as well as behavioral issues [52,58, 59] seems to be very common, which implies that a large proportion of the children with epilepsy exhibit cognitive and/or behavioral problems. The participants in this thesis might reflect especially this proportion of children and makes it possible to draw tentative conclusions for only this group.

Concerning the clinical behavioral questionnaires it represents a strength that these have different normative groups and they seem to be reliable and valid for children with epilepsy [60]. It is however difficult to capture subtle behavioral differences in daily life. Nevertheless, by combining the questionnaires with clinical observations during test assessment, it seems as that we were able to detect a large proportion of the problems identified by the caregivers. In the clinical field, discussing the results of the neuropsychological assessment, caregivers did mostly agreed with outcome. A limitation of this thesis is using the NVOS for parental burden. This questionnaire is less investigated and the validity can be questioned. The high association between experienced parental burden and reported behavioral problems, which was expected according to the literature, increases the validity of this questionnaire. The confirmation of the parents concerning the outcome, strengthen this hypothesis. At this point it needs to be repeated that parents' reports in general have to be interpreted cautiously because of the inconsistency. In this thesis we decided not to dismiss these reports, because the clinical observation, parents reports and part of the test assessment gave equal results and reinforced the total result.

Another important issue to keep in mind is the ecological validity of test assessment [61]. This is unfortunately sometimes poor, but there are not always many validated alternatives to investigate specific functions in young children. We did detect neuropsychological problems, which resembled parental reports and clinically observations and this integration of information reflects the strength of the total assessment. The proportion of children with deviant results on only test assessment were lower than might be expected and could be related to choice of tests. This might be especially true for working memory. In test assessment in this thesis we found no deficits, but using the BRIEF, we could confirm working memory deficits adding to the growing body of evidence that children with epilepsy exhibit working memory problems [62].

From a neurocognitive perspective, the construct of EF seems to broad to be meaningful. Executive functions are a large component of everyday functioning, but are difficult to identify using traditional tests. The strength of this thesis is unraveling an important part of the EF, the cognitive control. Although to some extent separable, the components of cognitive control (shift, inihite, working memory) share a common purpose: the allocation of attention and control over behaviour, in order to meet an adaptive goal [34] and can therefore not totally be seen as independent functions. Moreover, more recent factor analytic evidence suggests no specific factor for inhibition/inhibitory control [63]. It is proposed that inhibtion is entirely subsumed under 'common EF'. Furthermore, Miyake et al. [34] claim that shifting may also involve inhibition, in the form of reducing interference, as well as some elements of WM. This may explain the different outcomes of the different components in our investigation. However, Miyake and Friedman's conclusions are largely based on studies of young adults and therefore cannot be straightforwardly generalised to the structure of EF in young children [17]. Additionally, this thesis focuses only on cognitive control and its behavioral counterpart behavioral regulation, while it is clear that the association between different EF and behavior is broader than the cognitive control components we investigated.

Clinical implications

Unravelling different EF and its implications for daily behavior is in need for further research in children with (frontal lobe) epilepsy. Broad EF assessment is not always part of standard neuropsychological assessment, while it is clear that solid diagnostics can add tremendously in daily life in different settings, but also for treatment planning. Specific cognitive training and psycho-education can help e.g. in dealing with cognitive problems in daily life and reduce behavioral problems. Yet it is important to realize that it's not possible to capture the complete daily life functioning with traditional tests. Tapping different EF components will at least shed more light on the complete executive functioning. Social cognition problems for instance, may derive from the EF problems and are frequently clinically reported in children with FLE. Recent work shows that behavioral regulation and metacognition both contribute to social functioning in autism spectrum disorder (ASS) [64]. There are indeed many similarities between autism spectrum disorders (ASS) and epilepsy [27]. This might suggest that also for children with epilepsy, social cognition problems can have many implications for daily life functioning [26].
Another important aspect to consider in clinical daily work concerns obtaining information on parenting. In chapter 4, a bidirectional relationship between epilepsy, behavior and parenting is suggested. One of the missing links to confirm this, is parenting as well as personality assessment of the parents, which is (obviously) not part of the standard assessment. Findings from studies investigating both seizure and family variables as predictors of child behavior

show that family variables often have a greater influence [65]. Identifying these variables by using questionnaires related to parental burden and stress might give more insight in which parents are more at risk in developing parental stress and are more in need for specific interventions. Interventions based on this burden could have substantial implications; treating and/or (psycho-)educating parents might diminish behavioral problems as well as the experienced burden in an early phase.

Additionally, to identify groups more at risk, it is worthwile to consider different subgroups. In our group, variance in performance was large: the group as a whole performed worse on some tasks, but there were also children with good performance. Investigating this from another point of view, e.g. comparing bad and good performance, like we did with many and less perseverative errors on the WCST, might give more information on the question which group is most affected [62].

Because it's not always easy to capture daily life EF and because behavioral changes can occur in the absence of deficits on neuropsychological measures, it is essential to follow an integrative approach to combine traditional neuropsychological assessment, questionnaire data and clinical observations. Thereby, it is recommended that the different behavioral domains, as reported in proxy measures, be assessed with a current cognitive counterpart in order to accomplish an improved cognition- behaviour consistency [14]. Furthermore, since these children, in some cases, end up in mental health care institutions, it is important to distinguish between the classic DSM-V diagnosis and a DSM-V diagnosis based on behavioral changes by frontal lobe dysfunction, because the cause of the problems and therefore intervention might be different. This is an additional argument for identifying these problems at an early phase in order to start intervention which might help reduce psychopathology in children with FLE in the long term [66].

Lastly, research on direct links between structural prefontal cortex development and cognitive performance in infancy and early childhood is still limited. It is important to note that in order to establish a direct link between structural prefontal cortex maturation and early EF performance improvements, it would be necessary to conduct research that both obtains structural MRI recordings and behavioural data from the same cohort of infants [17]. This again stresses the importance to (neuropsychologically) assess these children at early age. A centre like our tertiary centre is ideally suited for this, as we have a large cohort that's early on in the picture and that will remain in treatment for years and frequently undergo imaging research.

Final considerations

When considering the forementioned evidence in this thesis, it can be suggested, from a behavioral perspective, that many children with FLE can become 'out of control', which cannot be classified as a psychiatric disorder and worsens growing up. The cognitive deficits as well as behavioral disturbances are merely explained by the underlying frontal pathology, which also induces the focal seizures. Developing interventions also based on cognitive control deficits and not only based on behavioral problems might improve current treatment. This research area lies at the intersection of developmental neuropsychology and psychiatry and is in line with the emerging view of cognitive neuropsychiatry that attempts to bridge this gap between psychiatric symptoms and neuropsychology within a framework of relevant brain structures and their pathology [67]. Future research therefore should focus not only on identifying epilepsy variables, but also on expanding assessment of cognitive and behavioral functions (especially social cognition) and need to take specific parent variables into account.

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NEDERLANDSE SAMENVATTING

Summary in Dutch

Achtergrond en inleiding

Epilepsie is een chronische neurologische aandoening gekenmerkt door frequente epileptische aanvallen. Kinderen met epilepsie in de frontaal kwab (FLE) kunnen daarnaast gedrags- en leerproblemen ontwikkelen. Dit kan zowel in de opvoeding voor de ouder als voor het kind zelf problemen opleveren. Specifiek kunnen de executieve functies (EF) aangedaan zijn. Deze EF vallen het best te omschrijven als functies die aansturend en controlerend zijn voor je hele doen en laten, zoals bijvoorbeeld de mate waarin gedrag kan worden geremd, er geschakeld kan worden tussen situaties. Hoewel er steeds meer kennis is over de onderliggende neuroanatomie en de specifieke cognitieve beperkingen, blijft de impact hiervan op het dagelijks functioneren bij kinderen met FLE grotendeels onduidelijk. Het belangrijkste doel van deze thesis is daarom dan ook om meer inzicht te krijgen in de relatie tussen EF problemen en gedragsproblemen bij kinderen met FLE in de schoolleeftijd. De thesis zal verschillende aspecten van EF en de gevolgen van EF problemen beschrijven. In deze samenvatting zullen de belangrijkste conclusies samengevat en bediscussieerd worden.

Deel I: Gedrag

De resultaten uit de review wijzen erop dat er een relatie is tussen EF problemen en gedragsproblemen bij kinderen met verschillende soorten epilepsie. Specifiek lijken problemen in de cognitieve controle en gedragsregulatie gerelateerd aan elkaar.

De eerste studie, die zich focust op de relatie tussen EF en gedrag bij kinderen met FLE, laat zien dat ouders en leerkrachten veel gedrags- en EF problemen rapporteren. Daarnaast is er sprake van een positieve relatie tussen deze EF problemen en gedragsproblemen, dat wil zeggen dat deze twee problemen met elkaar samenhangen. Een sterk punt in dit onderzoek is de overeenkomst tussen de rapportage van ouders en leerkrachten. Leerkrachten geven meer metacognitieve problemen aan, wat het best omschreven kan worden als het vermogen om zelfstandig taken uit te voeren en problemen op te lossen op basis van beoordeling van eigen gedrag. Ouders benoemen meer gedragsregulatie problemen, wat inhoudt in hoeverre een kind in staat is om flexibel te denken en emoties en gedrag te reguleren op basis van impulscontrole. De verschillen tussen de scores van ouders en leerkrachten zou verklaard kunnen worden uit de verschillende omgevingseisen die beide stellen aan een kind. Op school zijn er immers andere verwachtingen dan thuis en vice versa.

Uit de tweede studie, die zich richt op de ervaren last van ouders, blijkt dat vooral ouders van kinderen die al langer epilepsie hebben (meer dan 5 jaar) moeite ondervinden in de opvoeding van deze kinderen. Daarnaast is er een samenhang tussen deze ervaren last en de gedragsproblemen die gerapporteerd worden. Vooral meer externaliserend gedrag kan worden gerelateerd aan de last die ouders ondervinden. Een opvallende bevinding is dat ongeveer de helft van de ouders in deze studie niet erg consistent in hun antwoorden bleken te zijn, waar er geen sprake was van overmatige negatieve beoordeling over hun kinderen. Deze inconsistentie kan mogelijk deels verklaard worden uit epilepsiekenmerken, waarbij kinderen met epilepsie bijvoorbeeld ook meer variatie dan normaal in hun gedrag laten zien.

Deel II: Cognitie

Naar aanleiding van de bevindingen uit de review is er voor gekozen om dit deel van de thesis te richten op cognitieve controle. Dit omvat globaal genomen schakelen/cognitieve flexibiliteit, het werkgeheugen en inhibitie. In de derde en de vierde studie is dit onderzocht middels testonderzoek en vragenlijsten voor ouders. Hieruit blijkt dat kinderen met FLE met behulp van testonderzoek forse problemen met het schakelen van de aandacht laten zien en daarnaast een minder goed vermogen tot inhiberen hebben. Dit stemt overeen met de rapportage van ouders. Testonderzoek gericht op het werkgeheugen laat globaal dezelfde resultaten bij kinderen met FLE in vergelijking tot gezonde leeftijdsgenoten, waarbij ouders echter wel forse problemen rapporteren. Een opvallende bevinding uit deze twee studies is dat de ontwikkeling van EF meer afvlakt dan op basis van leeftijd verwacht wordt. Dat wil zeggen dat kinderen in de loop van de tijd (rond 11 jaar) op deze EF gebieden gaan achterlopen in vergelijking met gezonde leeftijdsgenoten, ook wel 'growing into deficit' genoemd.

Belangrijkste conclusies en aanbevelingen

Niet alle kinderen in deze thesis hebben (aantoonbare) hersenschade. Echter, EEG onderzoek toont frontale hersenproblematiek, waardoor kinderen met FLE vergelijkbare problematiek kunnen ontwikkelen zoals die ook gezien worden bij mensen met hersenletsel. Daarbij is er regelmatig sprake van aanvallen, waardoor het brein verstoord wordt en hiermee ook de hersenontwikkeling. De frontaalkwab wordt al lange tijd gelinkt aan EF en deze worden weer gerelateerd aan gedragsproblemen, ook wel het frontaalsyndroom genoemd.

Alhoewel deze link vaak gelegd wordt, is deze 1-op-1 relatie niet zo definitief als het klinkt. Nieuwe studies laten zien dat meerdere netwerken zijn in het brein, waardoor EF problemen mogelijk ook meer verklaard kunnen worden vanuit het samenspel tussen verschillende hersengebieden. Ondersteuning hiervoor is bijvoorbeeld dat ook niet frontale schade of epilepsie tot EF problemen kunnen leiden. Echter, opvallend in onze groep van kinderen met FLE is dat in de klinische praktijk regelmatig fors afwijkend gedrag wordt gezien, welke niet in die mate wordt gerapporteerd bij epilepsie met een andere focus. Dit gedrag vertoont overeenkomsten met pati√´nten met frontale hersenschade. Dit leidt tot de voorzichtige conclusie dat er, ondanks de netwerktheorie, zeker sprake kan zijn van functioneel verlies of beperkingen.

In deze thesis zijn er helaas geen specifieke epilepsie variabelen gevonden die bijdragen aan de gevonden resultaten. Dat wil zeggen dat het grotendeels onduidelijk blijft welke kinderen meer kwetsbaar zijn voor het ontwikkelen van

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deze problemen. Langer durende epilepsie en een vroeg debuut van aanvallen lijken wel risicofactoren te zijn.
Een belangrijk aspect bij onze specifieke groep is de slaapkwaliteit. Kinderen met FLE hebben vaak nachtelijke aanvallen en hierdoor een slechtere slaapkwaliteit. Onderzoek heeft al eerder aangetoond dat dit, in het algemeen, van invloed is op zowel cognitief als gedragsmatig functioneren. Helaas was hier geen data van en is dat niet meegenomen binnen deze thesis. Het is in de klinische praktijk wel opgevallen dat kinderen met een verbeterde aanvalscontrole in de nacht na medicatie aanpassing, beduidend minder gedragsproblemen lieten zien. Deze problemen verdwenen niet volledig, wat doet vermoeden dat niet alleen de aanvallen op zichzelf de oorzaak zijn van alle problemen, maar dat er een onderliggende conditie is die zowel de oorzaak is voor de epilepsie als voor de EF en gedragsproblemen.
Hoewel deze thesis slechts een beperkte positieve relatie vindt tussen testonderzoek en gedragsrapportage, is het desondanks gelukt om vast te leggen welke problemen er geobserveerd worden bij kinderen met FLE. Belangrijk voor de toekomst is dat er aanwijzingen zijn dat inhibitieproblemen op jonge leeftijd worden gelinkt aan problematisch gedrag op latere leeftijd. Gezien de gevonden inhibitieproblemen in huidig onderzoek lopen kinderen met FLE daarmee het risico om op latere leeftijd gedrags- en psychiatrische problemen te ontwikkelen. Vroege interventie zou dus latere problemen kunnen verminderen, mogelijk voorkomen.
Voorts lijkt vooral meer externaliserend gedrag gerelateerd aan de ontwikkeling van stress bij ouders. Aangezien de kinderen met FLE vooral dit soort gedrag laten zien, is er een groter risico op overbelasting van ouders. Ook hiervoor geldt dat vroege interventie richting ouders behulpzaam kan zijn bij het verminderen en voorkomen van problemen op latere leeftijd.

Al met al ontstaan er bij kinderen met FLE problemen die niet gezien kunnen worden als alleen een psychiatrisch beeld en welke kunnen verslechteren in de loop van de tijd. Zowel kind als zijn ouders kunnen dan ‘out of control’ raken. De onderliggende frontale problematiek lijkt niet alleen de oorzaak voor epileptische aanvallen, maar ook voor deze cognitieve- en gedragsproblemen.
Tot slot komt uit deze thesis naar voren dat het combineren van (neuropsychologisch) testonderzoek en gedragsvragenlijsten, naast observaties uit de klinische praktijk essentieel zijn in de diagnostiekfase. Daarnaast benadrukt deze thesis ook het belang om dit al op jonge leeftijd te doen en daarbij de relatie te leggen met het medisch onderzoek. Interventies gericht op zowel cognitie als gedrag bij ouder en kind kunnen de huidige behandeling verbeteren. Verschillende aspecten van EF zijn in deze thesis niet onderzocht, maar kunnen wel grote impact hebben op gedrag, zoals bijvoorbeeld sociale cognitie. Dit is een belangrijk onderzoeksonderwerp voor de toekomst.

DANKWOORD

Dankwoord

Lieve Olivier en Adrian, ik houd wel van een beetje onconventioneel en daarom begin ik dit dankwoord met jullie! Dat ik begin met jullie is niet helemaal toevallig. Zonder dat jullie het tot vandaag toe beseffen, ben ik al jullie hele leven met dit proefschrift bezig. Alhoewel dit er ook voor zorgt dat niet altijd alles even snel gegaan is zoals ik van mezelf gewend ben, heeft dit juist grote meerwaarde gehad. Thuis was ik mama, speelden we spelletjes en gingen we wandelen met onze hond Cody. Thuis stond ik 'uit', was er tijd voor relativeren en had ik pauze. Het pauzeren en kritisch naar mijn werk kijken was me waarschijnlijk zonder jullie niet zo goed gelukt! Ik hoop echter ook dat dit proefschrift jullie (later) inspireert, in de zin dat dromen echt uit kunnen komen, op welke, soms gekke, manier dan ook.
Alhoewel jullie nog niet begrijpen wat mama altijd op het werk aan het doen is, weten jullie wel waarom ik altijd zo voorzichting ben met jullie hoofd: 'daar zitten de hersens' zeggen jullie vaak. Toen je 3 jaar was, Adrian, had je het concept al begrepen; toen je iets deed wat niet mocht zei je: 'dat deed ik niet, dat deden mijn hersens'. Precies dit is de essentie van waarom ik ooit met dit werk als neuropsycholoog en later mijn onderzoek begonnen ben. Ik wilde zo graag begrijpen waarom we doen wat we doen en dit vooral naarmate mijn loopbaan zich vorderde ook goed overbrengen naar anderen.

Terwijl ik de laatste hand aan dit proefschrift leg is er ineens veel veranderd. De wereld verkeert in een crisis vanwege COVID-19, het corona virus. Helaas zijn veel mensen ziek en overleden, velen zullen nog ziek worden en overlijden. Hoe naar de dingen ook zijn die nu gebeuren, het zorgt er ook voor dat ik anders tegen bepaalde zaken aankijk en heroverweeg wat nou echt belangrijk is. De afronding van het onderzoek komt daarmee automatisch iets lager op de prioriteitenlijst. Dit maakt echter ook dat dit dankwoord misschien nog wel belangrijker is geworden dan wat het al was, meer uitspreken van waardering. Bij deze dan ook een dankwoord voor een ieder die heeft bijgedragen.

In de spreekkamer kwamen er steeds meer kinderen met soms bizar gedrag wat moeilijk te begrijpen was. Dit wilde ik gaan begrijpen en uitleggen aan de mensen die zo tegen dit gedrag aanliepen. Nu ik dit schrijf klinkt dit vrij makkelijk, de realiteit is helaas wat weerbarstiger gebleken; het ging niet vanzelf, soms makkelijk, soms moeilijk, soms een heel lange pauze. Dankzij vele anderen is het resultaat er dan eindelijk.

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om de kinderen na die tijd te ondersteunen, maar ook al die vragenlijsten in te vullen. Ook dank aan de leerkrachten van de kinderen die bereid waren om vragenlijsten in te vullen over de kinderen.
Ik had deze kinderen natuurlijk nooit kunnen werven voor mijn onderzoek zonder de onvoorwaardelijke steun van SEIN en specifiek die van Jan de Boer en Gert de Jonge. Vanaf het begin hebben jullie mij gesteund in het verkijgen van de KNP opleidingsplek en het doen van onderzoek en ook alles gefaciliteerd wat hiervoor nodig was. Zelfs nog een beetje meer. Mijn dank hiervoor is groot.

Dit proefschrift was er niet gekomen zonder Jaap. Prof. dr. Jaap van der Meere, ik weet nog goed dat we elkaar ontmoetten voordat ik uberhaupt met KNP opleiding begonnen was en alleen 'maar' een college kwam geven over epilepsie bij kinderen. Je vroeg of er niet iemand binnen SEIN geinteresseerd was in onderzoek. Dat dit zou leiden tot wat er nu ligt had ik nooit gedacht. Vele kilometers heb ik van en naar Groningen gereden, waarin we meer dan eens met elkaar discussieerden wat er wel en niet in de artikelen mocht staan en ik jou zelfs nog wat mocht leren over epilepsie! Je gaf me veel vrijheid in de onderwerpen en stelde hierover kritische vragen. Ten tijde van dit schrijven ben je vanwege COVID-19 gebonden aan Finland, gelukkig kunnen we elkaar zelfs dan goed bereiken. Je geduld met mijn pauzes is soms misschien aardig op de proef gesteld, maar ik hoorde niets anders dan begrip en steun. Ik kan je hiervoor niet genoeg bedanken. Dankjewel!
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Olivier en Adrian, dromen zijn uitgekomen.
Volg wie je wilt zijn en alles komt goed.
Nu is het klaar! Kom, we gaan wandelen.

D

ABOUT THE AUTHOR

Curriculum Vitae
List of Publications

Lydia van den Berg werd geboren op 25 september 1983 in Enschede. Met een kleine omweg startte ze de studie psychologie aan de Universiteit Twente in Enschede in 2002, al wetende dat ze in de medische richting wilde werken.
Ze vervolgde de opleiding in Utrecht de richting neuropsychologie en liep stage binnen het Medisch Spectrum Twente in Enschede. In 2007 behaalde ze haar master en kreeg bijna direct haar eerste baan als (kinder) psycholoog binnen revalidatiecentrum 'Het Roessingh' in Enschede. Sinds december 2007 is ze werkzaam bij SEIN, waar ze in 2011 na het afronden van de opleiding tot gezondheidszorgpsycholoog doorstroomde in de opleiding tot klinisch neuropsycholoog in 2012. Gedurende deze opleiding is ze met, in dit proefschrift beschreven, onderzoek gestart en werd ze bedrijfsvoerend hoofd van de afdeling psychologie binnen SEIN. In 2016 behaalde ze haar diploma als klinisch neuropsycholoog. Het wetenschappelijk onderzoek werd gecontinueerd en daarnaast werd ze tevens inhoudelijk hoofd van de afdeling. Momenteel is ze nog steeds werkzaam binnen SEIN als zowel clinicus als hoofd van de afdeling. Naast het aandachtsgebied kinderen houdt ze zich veel bezig met epilepsiechirurgie voor zowel kinderen als volwassenen. Buiten SEIN deelt Lydia haar enthousiasme en kennis voor haar vak binnen verschillende opleidingen (bachelor, master, GZ-opleiding, opleiding tot KP en KNP) en geeft ze supervisie.
In 2015 trouwde ze met Jachin Letwory. In 2014 werd haar zoon Olivier geboren en in 2016 haar zoon Adrian.

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