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The Danish Epilepsy Center Filadelfia

Family impact of Complex Childhood Epilepsy

PhD thesis

Anne Vagner Jakobsen



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FILADELFIA

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Submitted:	August 9th, 2021. Institute of Psychology, Faculty of Health Sciences, University of Southern Denmark, Odense, SDU.

FILADELFIA

Danish National Centre for Psychotraumatology

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University of Southern Denmark

To my parents;

In memoriam *Anna Lise K. Wagner*, and yet with us *Ejvind B. Ludvigsen*.

Their wisdom and ways of life still lead my path.

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Preface

This industrial PhD project results from a collaborative work between the Danish Epilepsy Center, Filadelfia, and The National Center of Psychotraumatology, Institute of Psychology, University of Southern Denmark, Odense, SDU. The project is funded by the Danish Epilepsy Center and The Danish Epilepsy Association with the aim of providing better care to families living with complex childhood epilepsy.

The project emerged from everyday clinical practice at the Danish Epilepsy Center. Children with complex epilepsy are referred to the center for a comprehensive neuropsychological evaluation to address the child's support needs. However, a limited focus has been addressed to parental resources even though parents need to be resourceful to meet their child's demands and follow up on our guidance.

Moreover, psychopathology is, just as behavioral difficulties and developmental disorders, commonly occurring sequelae to childhood-onset epilepsy. However, even though being critically ill can cause posttraumatic stress disorder (PTSD) and trauma exposure in childhood epilepsy is high, PTSD has not been assessed in line with other psychopathological disorders in children with complex epilepsy.

Although we have a limited understanding of the causations between illness characteristics and the associated sequelae, investigating trauma issues could bring a new perspective to this understanding as trauma reactions in children often manifest as behavioral problems, somatic complaints, and social withdrawal, which are well known in children with epilepsy.

Taken together, to provide better care of families living with childhood epilepsy, we needed to assess the support needs of parents in Denmark and to investigate if trauma in children with epilepsy might be a factor of concern alongside other psychopathological disorders.

Thus, this PhD project focuses on the mental aspect of living with complex childhood epilepsy assessing caregiver psychopathology and child trauma symptoms.

Acknowledgments

First, I want to thank all participating children and their parents for their invaluable time and insights. The extensive survey took time and effort, and I am deeply thankful that so many families welcomed the survey during a vulnerable time at the Danish Epilepsy Center Filadelfia.

Secondly, personal thanks are given to the former medical director at Filadelfia MD PhD Helle Hjalgrim for supporting the project idea. She had an understanding of the importance and timing of the project before I did. Further thanks are given to the neuropediatric department at the Danish Epilepsy Center, who embraced the project and supported the data collection on top of all other work tasks. Especially to team coordinator Sandie Louise Christensen for keeping me updated on all referrals and hospitalizations during the one-year-long data collection period.

Thirdly, I wish to express my gratitude to my primary supervisor Professor Ask Elklit for seeing the project's potential and patiently teaching me his field of expertise. His encouragement, wealth of field knowledge, and perspectives have led me confidently through the process. I feel fortunate to have been part of his positive and helpful lab at The National Center of Psychotraumatology, from which I have learned so much.

Fourthly, I would like to thank my co-supervisors, Associate Professor Marina Nikanorova and Professor Rikke Steensbjerre Møller, for their support, encouragement, and invaluable diagnostic insights and perspectives. Furthermore, I wish to thank my clinical supervisor in child neuropsychology PhD Nina Madsen Sjø, for her helpful perspectives and teaching me the value of psychometrics.

Finally, special thanks go to my loving husband for providing a home and marriage that supports my endeavors in life.

List of papers in appendices

Paper I (Appendix A)

Jakobsen AV, Møller RS, Nikanorova M, Elklit A. *The impact of severe pediatric epilepsy on experienced stress and psychopathology in parents*.

Epilepsy and Behavior Nov. 2020. DOI: 10.1016/j.yebeh.2020.107538

Paper II (Appendix B)

Jakobsen AV, Elklit A. *Post-traumatic stress disorder (PTSD) symptoms in children with severe epilepsy*.

Epilepsy and Behavior Aug. 2021. DOI:10.1016/j.yebeh.2021.108217

Paper III (Appendix C)

Jakobsen AV, Elklit A. *Self-control and coping responses are mediating factors for parental stress and family impact in caregivers of children with severe epilepsy*.

Epilepsy and Behavior Aug. 2021. DOI:10.1016/j.yebeh.2021.108224

Abbreviations

ADHD	Attention-deficit/hyperactivity disorders
AED	Antiepileptic drug
ASD	Autism spectrum disorder
CPTSD	Complex post-traumatic stress disorder
DMN	Default Mode Network
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSO	Symptoms of disturbances in self-organization (items in CPTD)
HPA	Hypothalamic-pituitary-adrenal axis
HRQoL	Health-related quality of life
mPFC	Medial prefrontal cortex
ICD	International Classification of Diseases
ILAE	International League Against Epilepsy
PTSD	Post-traumatic stress disorder
QoL	Quality of life
TLE	Temporal lobe epilepsy
WHO	World Health Organization

English Summary

Background and objectives

Epilepsy is one of the most common chronic neurologic conditions in children and affects 0.3-0.6 % during childhood. Caring for a child with complex epilepsy is a well-known predictor of mental distress and psychopathology in caregivers; however, the issues have not been investigated in Denmark.

When the physical and emotional demands of caretaking exceed parental resources, the entire family is affected, and optimal caretaking is challenged. The family often needs support to retain or regain their resources; however, little is known about how to support the families, and the evidence for existing intervention programs is low.

This PhD project aims to understand the support needs of families living with complex childhood epilepsy in a national context to provide better care and target interventions in clinical settings.

Methods

The research project is a single-center cross-sectional study. The study includes 162 caregivers of 140 children with complex epilepsies assessed by questionnaires and structured clinical interviews during the child's hospitalization at the only tertiary epilepsy center in Denmark; The Danish Epilepsy Centre, Filadelfia.

The study addresses three research questions; 1) the prevalence and associations of parental stress and psychopathology, 2) the prevalence of child trauma symptoms and psychopathology, and 3) the family impact of living with complex childhood epilepsy.

Results

The first study question reveals that symptoms of psychopathology are present in about half of the caregivers. We had expected a high prevalence; however, not at this level. Surprisingly, we find that the caregivers' resources and the degree of behavioral difficulties in the child, rather than epilepsy-related factors, have the highest impact on parents' mental distress and psychopathological symptoms. Therefore, caregiver resources and the degree of child behavior difficulties are essential to consider when assessing caregivers' support needs.

The second study question demonstrates a high level of trauma symptoms in children with complex epilepsy, specifically in schoolchildren and adolescents. These results are concerning; although, more extensive studies have to confirm the findings. The study on trauma symptoms in children with complex epilepsy with developmental-sensitive and standardized tests is the first of its kind to the author's knowledge. Preschoolers did not express elevated levels of trauma symptoms; however, comorbid psychiatric symptoms were present in four out of five children under seven years. Behavioral difficulties were elevated across all ages, and we found a high concurrency of parental psychopathology and child trauma symptoms. Assessing trauma exposure and the experience of trauma in children with complex epilepsy might further clarify the complex associations of biological and contextual variables that affect the children's life quality and may enable better preventative treatment options for this group.

The final study question examines the family impact of complex childhood epilepsy and the mediating role of parental individual psychological factors. Parental sense of control and the degree of emotional coping response mediated the relationship between child behavioral difficulties as a proxy measure of epilepsy severity and family impact and parental stress. Social support ceased to be a protective factor for parental stress in the presence of lower levels of self-control and higher emotional coping responses. The significant influence of self-control is highly relevant when assessing the needs

for support in the families. The sense of control might be a specific challenge for caregivers of children with complex epilepsies, as epilepsy is a highly unpredictable condition.

Perspectives

This PhD project contributes with new knowledge in a national and international perspective concerning the impact of living with complex childhood epilepsy. The study results have demonstrated a significant need for support and treatment options in families with a child with complex epilepsy. No formalized family intervention is available in Denmark, advocating for future research into family programs based on the acquired knowledge from this study.

Research concerning trauma exposure in childhood epilepsy and how children experience and react to the inevitable adverse events in the more complex and severe epilepsies would further help address the support needs of the families.

Dansk resume

Baggrund og formål

Epilepsi er en af de mest almindelige kroniske neurologiske lidelser hos børn, og opstår hos 0.3-0.6 % af alle børn i løbet deres barndom. Det er velkendt, at forældre til børn med en sværere form for epilepsi oplever, at blive betydeligt påvirket af deres barns sygdom, og de følger som epilepsien medfører, men området er ikke belyst blandt danske forældre.

Når de fysiske og følelsesmæssige krav i håndteringen af barnets epilepsi overstiger forældrenes ressourcer, får forældrene sværere ved at varetage deres barns behov, og hele familien påvirkes. Familien har ofte brug for støtte til at bevare eller genvinde deres ressourcer, men der eksisterer kun sparsom viden om hvordan familierne kan hjælpes. Ligeledes findes der kun sparsom evidens for virkningen af eksisterende interventionsprogrammer for familier til børn med epilepsi.

Dette ph.d.-projekt sigter mod at få en bedre forståelse for de støttebehov familier til børn med en sværere form for epilepsi har i en national kontekst for bedre at kunne målrette støtteforanstaltninger i klinisk regi.

Metode

Forskningsprojektet er en tværsnitsundersøgelse udført på Danmarks eneste tertiære epilepsicenter; Epilepsihospitalet Filadelfia. Undersøgelsen er foregået ved besvarelse af spørgeskemaer og strukturerede kliniske interviews under barnets indlæggelse på Epilepsihospitalet, og omfatter 162 forældre til 140 børn med en sværere form for epilepsi.

Undersøgelsen vedrører tre forskningsspørgsmål; 1) forekomst af stress og psykopatologi hos forældre samt associerede sammenhænge, 2) forekomst af traumesymptomer og psykopatologi hos børnene, og 3) påvirkning af familielivet når et barn har en sværere form for epilepsi.

Resultater

Resultaterne af første forskningsspørgsmål viser, at godt halvdelen af forældrene i undersøgelsen har symptomer på angst, depression eller PTSD. Vi havde forventet en høj forekomst, dog ikke på det niveau. Overraskende ses det, at forældrenes ressourcer og graden af adfærdsmæssige vanskeligheder hos barnet har større indflydelse på forældrenes psykopatologiske symptomer end epilepsirelaterede faktorer. Det er derfor væsentligt at være opmærksom på forældrenes grad af ressourcer og adfærdsmæssige vanskeligheder hos barnet, når familiernes støttebehov skal vurderes.

Det andet forskningsspørgsmål påviste et højt niveau af traumasymptomer hos børn og unge med en sværere form for epilepsi. Resultaterne er af bekymrende karakter, om end der er behov for mere omfattende undersøgelser for at bekræfte resultaterne. Undersøgelse af traumasymptomer hos børn med kompleks epilepsi med udviklingssensitive og standardiserede tests er så vidt vides ikke udført tidligere.

Der blev ikke fundet forhøjede niveauer af traumesymptomer hos små- og førskolebørn, men fire ud af fem børn under syv år udviste øvrige komorbide psykiatriske symptomer. Endvidere påviste resultaterne adfærdsmæssige vanskeligheder hos børnene uanset alder, og der sås et højt sammenfald af traumersymptomer hos børnene og psykopatologi hos forældrene.

Vurdering af traumeeksponering og traumereaktioner hos børn med epilepsi kan muligvis bidrage med bedre forståelse af det komplekse samspil mellem biologiske og kontekstuelle variabler, som påvirker børnenes livskvalitet. En bedre forståelse vil endvidere muliggøre forebyggende tiltag og optimere behandlingsmuligheder rettet mod metal mistrivsel hos børnene.

Det sidste undersøgelsesspørgsmål påviste at forældrenes individuelle psykologiske faktorer har indflydelse på hvor stressede de oplever at være og hvor stor indflydelse barnets adfærdsmæssige vanskeligheder har på familielivet. Forældres oplevelse af at være i kontrol i eget liv og grad af følelsesmæssig coping respons, medierede forholdet mellem børnenes adfærdsmæssige

vanskeligheder og oplevelsen af hvordan familielivet bliver påvirket samt forældrenes niveau af stress. Social støtte ophørte med at være en beskyttende faktor for forældrestress når forældrene oplevede lavere niveau af kontrol og højere grad af følelsesmæssig coping respons.

Følelsen af at være i kontrol i eget liv kan være en specifik udfordring for forældre til børn med sværere former for epilepsi, da epilepsi er en uforudsigelig sygdom. Det er derfor væsentligt at være opmærksom på hvordan forældrene oplever at være i kontrol, når familiernes støttebehov vurderes.

Perspektivering

Dette Ph.d. projekt har tilvejebragt ny viden i et nationalt som internationalt perspektiv om den belastning familier oplever når et barn har en sværere form for epilepsi. Resultaterne vidner om et betydeligt behov for støtte og behandlingsmuligheder hos familierne, om end ingen formaliserede interventionsmuligheder er tilgængelige i Danmark. Diskrepansen imellem den høje belastning i familierne, og de manglende interventionsmuligheder understreger behovet for fremtidig forskning omkring familieorienterede interventioner, baseret på den erhvervede viden denne undersøgelse har frembragt.

Yderligere forskning vedrørende traumeeksponering og traumereaktioner hos børn med en sværere form for epilepsi vil endvidere hjælpe med at få forståelse for, og at kunne imødekomme, familiernes støttebehov.

1. Introduction

Epilepsy is one of the most common chronic neurologic conditions in children and affects 0.3-0.6 % during childhood (Camfield & Camfield, 2015). Caring for a child with complex epilepsy is demanding, and parents' mental distress, fears, and sorrow are natural reactions when a child acquires a chronic health condition. However, when the physical and emotional demands of caretaking exceed parental resources, the entire family is affected, and optimal caretaking is challenged. The family often needs support to retain or regain their resources; however, little is known about how to support the families, and the number and evidence of existing intervention methods are limited (Duffy, 2011; Fleeman & Bradley, 2018; Law, Fisher, Fales, Noel, & Eccleston, 2014).

This PhD project aims to understand the support needs of families living with complex childhood epilepsy to provide better comprehensive care and target interventions in clinical settings.

This chapter starts by outlining how 'complex childhood epilepsy' is understood from a contextual perspective, followed by the current knowledge about the impact of living with complex childhood epilepsy for parents and the affected child. Finally, the chapter provides insight into the neurobiology of trauma and PTSD in children, how to assess it in children, and why it is specifically of interest to investigate within childhood-onset epilepsy.

1.1. Theoretical background

1.1.1. A definition of Complex Childhood Epilepsy

The terms severe, complex, and complicated childhood epilepsy are used interchangeably in the scientific literature; however, no globally accepted clinical definitions have been designated to the terms (Dunn, Buelow, Austin, Shinnar, & Perkins, 2004). In the ongoing update of the International League Against Epilepsy (ILAE) Classification of the Epilepsies, the use of the word 'benign' and 'catastrophic' epilepsy are no further recommended as appropriate terms for a diagnostic

label or category of epilepsy syndromes (Berg et al., 2010; Scheffer et al., 2017). The first is due to the strong emotional overtones of the word and the second for misleading physicians, patients, and families concerning the often associated sequelae of 'benign' epilepsies, including cognitive decline, behavioral difficulties, and psychiatric illnesses. The ILAE task force working on the update suggests the term "benign" is replaced by the two terms self-limited, which refers to anticipated spontaneous resolution of a syndrome, and pharmacoresponsive, where the epilepsy syndrome is anticipated to be controlled with appropriate antiepileptic therapy (Scheffer et al., 2017).

The concept of epileptic encephalopathy has previously been used as a term for the most severe epilepsies with onset in infancy and early childhood. The term has further been redefined and is suggested to apply to epilepsies at all ages (Berg et al., 2010). Recognizing the heterogeneity of epilepsy syndromes associated with encephalopathy has resulted in a more nuanced description of the term. The terms are developmental encephalopathy and epileptic encephalopathy, or the two used jointly. The ILAE task force proposes that developmental encephalopathy is used where there is just developmental impairment without frequent epileptic activity associated with regression or further slowing of development. Epileptic encephalopathy is meant to describe the syndromes where the epileptiform activity can cause regression or developmental plateauing above and beyond what might be expected from the underlying pathology alone. The impairments are suggested to be seen along a spectrum of severity. In cases where both factors play a role, the terms can be used jointly (Scheffer et al., 2017).

The work of the ILAE task force accentuates the importance of a precise definition of the terminology used for classifications of epilepsies to avoid misconceptions of the terms. In particular, the redefinition and exclusion of terms that could lead to an imprecise judgment of the severity of the various syndromes based on etiology and physiological indicators have seemed to be an essential part of the work.

Although no official clinical definition of severity classification of epilepsy exists, and the ILAE task force have adjusted the terms that previously classified some conditions into severe (catastrophic) and not severe (benign) types of epilepsies, the severity of illness have long been evaluated on a spectrum for multiple purposes.

Stein and colleagues proposed a framework for approaching illness severity in 1987. Functional severity and the burden of illness were two equal areas of measure when addressing the severity of illness (Stein et al., 1987). Functional severity points to the impact of the illness or disorder on an individual's ability to perform age-appropriate activities, concerning the mediating effect of physiological and psychological factors on functioning. The burden of illness addresses the impact of the disease or condition on the family or society. The authors stated that 'severity is not an absolute or universal concept' and that 'distinct constructs (of severity) are useful in different contexts' (p. 1508). The framework brings awareness to the paradox in measuring the severity of illness, highlighting different perspectives between clinicians, families/society, and the patient herself. The clinicians may primarily target the physiological aspect of the condition, while families may be concerned about the burden of illness and the patient on functional impairments. The authors further address the poor correlations between the indicators of severity. A child with a developmental disability may not need frequent hospital admissions; thus, the severity is low in terms of medical-care costs. However, if a parent cannot work and the family is limited in its activities due to the disability, the severity may rate high within the family. Likewise, the severity may be rated high within a societal context if the family has many support needs or the child requires admission to an institution for children with special needs.

The authors offer the following guidelines on the use of the term severity: '*1. Specify the nature of the construct the measure is intended to assess, whose perception of severity is being considered, the reference interval, and the purpose of the measure; 2. Because few measures have been validated*

against a gold standard, use more than one whenever possible for maximum validity; 3. Within disease categories, be alert to factors that may alter the underlying physiological indices; 4. When comparing severity of different conditions, do this at the level of functional status or burden of illness.' (p. 1509). These guidelines and the methodological considerations of measuring illness severity seem highly relevant today when addressing the severity of epilepsy in children.

In the following decade, numerous rating scales of seizure severity and other single severity measure scales were developed and used in clinical practice and research purposes (Baker et al., 1991; Carpay et al., 1996; O'Donoghue, Duncan, & Sander, 1996).

However, an attempt to classify the severity of various seizure conditions in children with epilepsy in a broader perspective was first made by Dunn and colleagues in 2004 (Dunn et al., 2004). The authors argue for the importance of rating the severity of the seizure condition to document therapy outcomes and predict psychosocial problems. They acknowledge that several factors contribute to the concept of condition severity, including seizure severity, epileptic syndrome severity, the number and side effects of antiepileptic drugs (AEDs), and the impact on the children and families. The authors used a Delphi technique[1] (Dalkey & Helmer, 1963; Linstone, Turoff, & Helmer, 1975) to establish the Epilepsy Syndrome Severity Scores for Children's Epilepsy (ESSS-C) for various ILAE pediatric epilepsy syndromes. Pediatric neurologists rated 36 different epilepsy syndromes on a scale from 1 to 10 across three domains: (a) response to medical treatment, (b) seizure severity, and (c) long-term prognosis. Although the various syndromes each were allocated a digit for severity, the authors did not provide a cut-off measure of when a syndrome is thought of as severe. Despite the thorough work in classifying the extensive list of childhood syndromes, other research groups have not attempted to validate the scale to the author's knowledge.

[1] The Delphi technique is a systematic and qualitative method, developed as an interactive forecasting method by collecting opinions from a group of experts through several rounds of questions.

A few years later, Speechley and colleagues developed a single-item, 7-point global rating scale designed for neurologists to assess the overall severity of epilepsy in children; the Global Assessment of Severity of Epilepsy (GASE) Scale (Speechley et al., 2008). The scale measures epilepsy severity from 1 (not severe at all) to 7 (extremely severe). During the initial construct validation of the single-item scale, seven clinical aspects of epilepsy were selected to test the convergent validity of the scale. These aspects were; frequency of seizures, the intensity of seizures, falls or injuries during seizures, duration/severity of the postictal period, total dose/number of antiepileptic drugs, side effects of antiepileptic drugs, and interference of epilepsy or drugs with daily life activities. All aspects were significantly associated with the GASE scale; however, frequency of seizures stood out as the individual aspect of epilepsy, explaining the most variance in severity of epilepsy as perceived by the clinician, with a nearly linear relationship between frequency of seizures and severity of epilepsy. The validity and reliability of the scale were later assessed with moderate to strong correlations with clinical aspects (Chan, Zou, Wiebe, & Speechley, 2015) and have been used in research studies in Canada (Goodwin, Wilk, Karen Campbell, & Speechley, 2017; Klajdi Puka, Ferro, Anderson, & Speechley, 2018).

At the same time, Humphrey and her colleagues developed the Early Childhood Epilepsy Severity Scale (E-Chess) to quantify the severity of epilepsy in infants and young children with tuberous sclerosis (Humphrey, Ploubidis, Yates, Steinberg, & Bolton, 2008). The scale comprises six severity items with three ordinal answer possibilities ranked 0 to 3, with higher scores indicating a higher severity. The items resemble those used for the construct validity work of the GASE scale with a few exceptions; seizure frequency; the number of seizure types; the period over which seizures occurred; the occurrence and duration of status epilepticus; the number of anticonvulsant medications used; and response to treatment. Further validation of the scale has to the author's knowledge not been undertaken; however, the measure is used in research settings across the world and is not limited

to measure epilepsy severity in children with tuberous sclerosis alone (Ahmed, Darwish, Khalifa, & Khashbah, 2020; Larson et al., 2012; Sehgal et al., 2017).

Based on the methodological considerations of Stein and colleagues and the current work of the ILAE task force, the title word of this thesis, 'complex childhood epilepsy' is chosen deliberately to accommodate the various perspectives of severity beyond the physiological measures of epilepsy and to avoid eventual misinterpretation of the word 'severe'. Complex childhood epilepsy implies a condition that is the opposite of simple. However, the term should not be misidentified as synonyms for epilepsy with simple or complex partial seizures. Complex childhood epilepsy is, in the context of this work, a term for children with epilepsy that is difficult to treat or who need specialist care in a hospital setting.

The titles of the three PhD papers include the term 'severe childhood epilepsy', which acknowledges the common historical frame of reference. However, with the clarifications above, 'complex childhood epilepsy' would be a more appropriate term for the group included in this study.

Just as the term 'severity' is a construct that depends on contextual factors and who defines it, 'sequelae' of complex childhood epilepsy may to some extent be contextually defined. The following section briefly addresses this issue and the implications of how sequelae are assessed.

1.1.2. Sequelae of childhood epilepsy

In the pioneering population-based Isle of Wight study by Rutter, Graham, and Yule (1970), psychiatric difficulties were found to be significantly higher in children with 'illnesses in the brain' compared to the general population and children with illnesses 'not involving the brain' (Graham & Rutter, 1968; Rutter, Graham, & Yule, 1970). Twenty-nine percent of children with uncomplicated

epilepsy[2] aged 5-14 years attending school were identified to have a psychiatric disorder compared with 6.6 % of children in the general population. The prevalence of the psychiatric disorder in children with seizures associated with cerebral palsy or some other structural brain disorder was 59 %. Moreover, a significant association between family influences and psychiatric disorders in children with epilepsy was found. Mothers of epileptic children with a psychiatric disorder were more likely to complain of emotional and psychosomatic complaints such as irritability, loss of temper, worrying, depression, and headaches, than mothers of epileptic children with no psychiatric disorder (Graham & Rutter, 1968).

Presently, and almost five decades later than the Isle of Wight study, a Norwegian nationwide registry study found approximately the exact prevalence of psychiatric/developmental disorders for complicated and uncomplicated epilepsy[3] compared to the general population (62.1 %, 15.8 %, and 6.6 %, respectively) (Aaberg et al., 2016). The registry study demonstrated that 78.3 % of children with epilepsy had ≥ one comorbid disorder. In 55 % of the children, other medical disorders were recorded, and neurologic disorders were found in 41 %. Children with complicated epilepsies were found to have the highest overall levels of comorbidity; however, children with uncomplicated epilepsies were likewise found to have a substantial risk of medical and psychiatric comorbidities (Aaberg et al., 2016).

The prevalence recurs in a review by Reilly and colleagues (2013) based on population studies of psychopathology in children with epilepsy. Approximately 30 % of children with uncomplicated epilepsy[4] and 50 % of children with complicated epilepsy are found to meet the diagnostic criteria for a behavioral or psychiatric disorder (Reilly, Kent, & Neville, 2013). The prevalence of behavioral

[2] 'Uncomplicated epilepsy' was defined as idiopathic epilepsy or epilepsy without any underlying brain lesion.

[3] 'Complicated epilepsy' is defined as childhood epilepsy with any additional diagnoses of neurologic disorders, intellectual disability, autism or other disorders of psychological development, and/or lack of expected normal physiologic development. 'Uncomplicated epilepsy' is defined with no such additional diagnoses.

[4] No definition for uncomplicated or complicated epilepsy was provided.

difficulties is significantly higher in children with epilepsy than children with other chronic health conditions or children from the general population. The review highlights significant associations between childhood epilepsy and attention-deficit/hyperactivity disorder (ADHD), depressive, and anxiety disorders. Moreover, there is a higher risk for autism spectrum disorder (ASD) in children with epilepsy than in the normal pediatric population. Additionally, ASD was found to be associated with significant intellectual disability.

The review included one study that provided parental and child measures of psychiatric 'caseness'[5] and depression scores in children (Turky, Beavis, Thapar, & Kerr, 2008). Parental measures were significantly higher than self-reported child measures. Parent ratings of child depression in children aged 5-17 years were 39,6 %. In children aged 11 years and above, the parent rating was 40 % compared to 23.1 % in child self-report ratings (aged ≥ 11 years). Parents rated psychiatric caseness to be 40 % in children aged 11 years and up (47.9 % in all included children aged 5-17 years), compared to 25.8 % in the child self-report (Turky et al., 2008).

A second study provided a prevalence of psychosocial problems in children, measured by parents, teachers, and child self-report (Høie et al., 2006). Psychosocial problems were commonly occurring and more common among children with epilepsy than controls by teachers and parents with odds ratios of five and nine, respectively. In addition, psychosocial problems were significantly related to epilepsy variables such as epilepsy syndrome, primary seizure type, age at onset, and seizure frequency. Interestingly, mothers and teachers reported males with epilepsy as having more problems than females; however, only females self-reported psychosocial problems, males did not (Høie et al., 2006).

Berg, Altalib, and Devinsky (2017) have recently discussed the challenges of assessing psychiatric and behavioral comorbidities in childhood epilepsy (Berg, Altalib, & Devinsky, 2017).

[5] Psychiatric 'caseness' is defined by scores of the Strengths and Difficulties Questionnaire (SDQ) on the basis of the combination of raised symptom (≥ 14) and impact (≥ 2) scores.

The authors argue that many existing studies on behavioral difficulties in childhood epilepsy rely on parent-proxy completed instruments to assess the level of difficulties. However, these proxy reports may reflect parents' reactions and emotions more than the child's difficulties, and the inherent bias highlights the need to assess children directly for more accurate measures. Further concerns are related to peri-ictal phenomena[6] that may be mischaracterized as underlying mood disorders. Additionally, according to the authors, the proposed bi-directionality[7] between epilepsy and psychiatric morbidity is based on reports of elevated levels of psychiatric morbidity before and after the diagnosis of epilepsy. They propose that psychogenic nonepileptic seizures (PNES) may account for some of the research findings associated with the proposed bi-directionality (Berg et al., 2017).

Although causal relationships may not be addressed, register studies and studies based on clinically assessed psychiatric disorders such as the Isle of Wight and Norwegian studies mentioned above emphasize a mental vulnerability associated with childhood-onset epilepsy.

Moreover, elevated risks of developing psychiatric disorders in adolescence and early adulthood have been associated with childhood-onset epilepsy. A Danish register-based nationwide cohort study of children presenting with seizures in childhood demonstrated an excess risk of developing psychiatric disorders such as anxiety, mood disorders, and psychotic disorders in adolescence and early adulthood (Dreier, Pedersen, Cotsapas, & Christensen, 2019). The association between epilepsy and psychiatric disorders later in life seemed to become stronger with the later onset of epilepsy.

[6] Peri-ictal relates to phenomena just before (pre-ictal), during (ictal) or after (post-ictal) seizures but are different from inter-ictal which means between (unrelated to) seizures.

[7] The hypothesis of bi-directionality between epilepsy and psychopathology was originally used to describe the links between epilepsy and depression. The bidirectional hypothesis suggests a shared genetic etiology between epilepsy and psychiatric conditions. It is founded on observations of people with epilepsy (PWE) are at increased risk of psychiatric disease, and vice versa, and that relatives of PWE are at a heightened risk for psychiatric disorders in addition to epilepsy (Berg, Altalib & Devinsky, 2017).

Recognizing the concerns of Berg and colleagues and the evidently high reports of child behavioral difficulties and psychopathology stress the importance of understanding the parental impact of caring for a child with epilepsy.

1.1.3. Parenting a child with epilepsy

Parents of children with a chronic or life-threatening illness such as complex childhood epilepsy are challenged by uncertainties associated with the condition and its implication on all aspects of life. The unpredictable nature of epilepsy is not limited to the unexpected subsequent seizure but also the unknown consequences of each seizure and the trajectory of the condition.

The personal impact of caring for a child with epilepsy is high. Psychopathology such as depression, anxiety, and post-traumatic disorder (PTSD) is common in parents across all types of epilepsy diagnoses (Carmassi et al., 2019; Iseri, Ozten, & Aker, 2006; Puka, Ferro, Anderson, & Speechley, 2019). Recent systematic reviews report clinical anxiety symptoms in up to 58% of parents (Jones & Reilly, 2016), and up to 50% of mothers show symptoms of depression (Ferro & Speechley, 2009). PTSD in parents of children with epilepsy is less investigated, and the prevalence varies between 4.5 % in fathers (Carmassi et al., 2018) up to 31.5 % in a combined group of parents (96% mothers) (Iseri et al., 2006). The prevalence of anxiety and depression in parents of children with epilepsy is equivalent to the prevalence in parents of chronically ill children in general and higher than in parents of healthy children (Cohn et al., 2020). The prevalence of PTSD is difficult to compare to other populations due to the few studies that have assessed the prevalence of parental PTSD in childhood epilepsy and the significant variability between the studies. However, a recent meta-analysis revealed an average PTSD prevalence of 18.9% in parents of children and adolescents with chronic physical illnesses (Pinquart, 2019).

It has been proposed that impaired parental mental health may increase the levels of parenting stress because of difficulties with meeting the child's needs (Abidin, 1990). Reversely, high levels of parenting stress may lead to mental health problems in the caregivers (Abidin, 1992). General parental stress and health-related parenting stress in parents of children with epilepsy have been a broadly investigated issue since the first studies of parental stress in childhood epilepsy were conducted in the early 1990s (Levin & Banks, 1991). Several reviews and meta-analyses have recently been conducted concerning parental stress and childhood illnesses, and two studies have included childhood epilepsy in their analyses (Cousino & Hazen, 2013; Pinquart, 2018).

Parental stress in studies on childhood illnesses is measured either as general parenting stress as by the widely used Parenting Stress Index (PSI) (Abidin, 1995), which measure stress within the parent-child system, or health-related parenting stress related to child health and behavior, such as the Child Health Questionnaire (CHQ-CF) (Landgraf, 2014) among others.

The general findings from the two reviews suggest that caregivers of children with a chronic physical condition have significantly greater levels of general parenting stress than caregivers of healthy peers (Cousino & Hazen, 2013). Moderate elevations in general and health-related parenting stress have been found in parents of children with epilepsy (Pinquart, 2018).

The two reviews differ from each other related to the impact of child and condition characteristics on parenting stress. The latter review finds that child characteristics are significantly associated with parental stress, which is not found in the Cousino and Hazen review. Higher levels of parenting stress were associated with greater severity of the child’s condition, and longer duration was associated with lower levels of health-related parenting stress. Further, parents of older children had lower levels of health-related parenting stress but higher levels of general parenting stress.

The review by Pinquart (2018) also reports less parenting stress if parents were married or cohabiting and higher perceived social support was associated with lower levels of parenting stress.

However, parental mental health and child behavior problems were the strongest correlates of parenting stress overall (Pinquart, 2018). The Cousino and Hazen review found that higher general parenting stress was associated with greater parental responsibility for treatment management (Cousino & Hazen, 2013).

General pathological stress not explicitly related to parenting has been less studied; however, a population-based study by Reilly et al. (2018b) assessed general stress in parents of children with epilepsy controlled against children with non-epilepsy neurodevelopmental disorders (Reilly et al., 2018b). The study finds that mothers of children with epilepsy were significantly more likely to be at-risk than the control group. Fathers did not differ between the epilepsy group and the control group; however, more fathers were in the at-risk range than would be expected compared to a normative sample.

Another area of research, however, less investigated than psychopathology and stress, is the quality of life (QoL) as a term in parents of children with epilepsy. Generally, QoL is a contextual term that may vary significantly in its measures, depending on which perspective is taken. According to the World Health Organization (WHO), QoL is a multidimensional construct defined as ’an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns’ (World Health Organization, 2021).

A recent review concluded that parents of children with epilepsy had a more inferior quality of life than healthy controls or population norms, however similar QoL as parents of children with other chronic conditions (Puka, Tavares, Anderson, Ferro, & Speechley, 2018).

The most often used questionnaire to measure QoL in parents of children with epilepsy is the Short Form Health Survey (SF-36) questionnaire or the shorter forms SF-12/SF-6D, which measure health-related QoL. The SF-36 targets vitality, physical functioning, bodily pain, general health

perceptions, physical, emotional, and social role functioning, and mental health (Ware & Sherbourne, 1992). The shortcoming of these questionnaires is the emphasis on parental health and not the impact of the child's health on parental QoL. Namely, how the parent's physical and mental health limit social activities, work, and everyday life. The mental health section seems to be the best proxy measure of the impact of the child's epilepsy on parental QoL and separates parents of children with epilepsy from controls (Puka, Tavares, Anderson, Ferro, & Speechley, 2018). A strength of the SF-36 questionnaire is that it points out to what degree emotional disturbances affect everyday life, according to the parent.

Another health-related QoL questionnaire used more often than other questionnaires is the WHOQOL-BREF (shorter version EUROHIS-QOL-8) (World Health Organization, 2021), similar to SF-36 measuring parental health-related QoL. However, the questions are not explicitly related to how parents experience how physical and mental health limit social activities, work, and everyday life. The questions are open for interpretation of any factor influencing health-related QoL. Additionally, the WHOQOL-BREF includes questions about the satisfaction of sleep quality, social support, and sufficient access to health services. These latter subjects are also investigated as single target measures in other studies, which are described below.

A few studies have investigated QoL in parents, mainly related to the child's condition. These studies are concerned with family QoL (Liu et al., 2020; Yuka et al., 2017), QoL related to the positive and negative aspects of caregiving (Jain et al., 2018), and the impact of childhood illness on the parent (Filho, Hoare, & Gomes, 2006; Sherman et al., 2008). Although the latter mentioned parental impact is measured by the Impact of Childhood Illness Scale (Hoare & Russell, 1995), the scale output is a total score, including impact on the child and family.

Caregivers highlight sleep quality and fatigue as some of the most critical areas of impact when parenting a child with severe epilepsy (Jensen et al., 2017). Parents of children with epilepsy have

significantly higher levels of sleep disturbances than healthy controls (Cottrell & Khan, 2005; Larson et al., 2012; Shaki, Goldbart, Daniel, Fraser, & Shorer, 2011), however equivalent to children with nonepilepsy-related neurodisability (Reilly et al., 2018b). Poor sleep quality has further proved to be significantly associated with maternal mental-health problems in mothers of children with epilepsy (Reilly et al., 2018a; Tsai, Lee, Lee, Jeng, & Weng, 2020).

The term 'family burden' of living with childhood-onset epilepsy have been investigated extensively for a variety of general impact factors such as family functioning (Braams et al., 2018), impact on siblings (Ostendorf & Gedela, 2017), and interrelationships within the family (Nolan, Camfield, & Camfield, 2006), social-relational impact outside the family (Gallop et al., 2010) and a financial burden (Jennum, Sabers, Christensen, Ibsen, & Kjellberg, 2017).

The social-relational impact inside and outside the family is high in families living with childhood epilepsy, and reversely, social support is often measured as a mediating and protection factor of the impact of childhood epilepsy on parental well-being (Carlson & Miller, 2017; Decker, 2014; Pinquart, 2018).

Camfield, Breau, and Camfield (2001) developed a childhood epilepsy specific 11-item questionnaire targeting the psychosocial impact of pediatric epilepsy on the child and family (IPES) (Camfield, Breau, & Camfield, 2001), which have been validated and used in different parts of the world (Gomez, Concepcion, & Garcia, 2012; Lv et al., 2009). It measures the overall health and QoL of the child, relationships with parents, peers, and siblings, social impact, and impact on family activities. However, despite the aim of measuring psychosocial impact on the family, it has been used interchangeably as a measure of child health-related QoL (Brabcova et al., 2021; Tanriverdi, Mutluay, Tarakci, Guler, & Iscan, 2016).

The financial burden of living with a child with epilepsy is substantial in countries where medical costs to some degree are self-paid (Gibson, 2014; Hussain et al., 2020), although, may be

comparable to that of other childhood illnesses (Khanna, Prabhakaran, Patel, Ganjiwale, & Nimbalkar, 2015). In addition, increased indirect costs of childhood epilepsy in the sense of reduced working hours or leaving the labor marked due to the child's condition are also regularly reported (Allers et al., 2015; Ana & Luis, 2004; Riechmann et al., 2015).

Because various perspectives and assessment tools have been used to address the impact of childhood epilepsy on family life and that the term 'family burden' is broadly defined, it is challenging to compare associations across studies. Furthermore, psychopathology and QoL of both parents and children may always be confounding factors of the perceived burden of illness in the family if not included in the measures. Hence, it is essential to reflect on what is targeted when measuring the family impact of childhood epilepsy.

A broader multi-area illness-directed assessment tool measuring family impact has only recently been adopted in childhood epilepsy-related research with the Impact on Family Scale (IFS) (Dehn, Korn-Merker, Pfafflin, Ravens-Sieberer, & May 2014). The scale assesses social/familial impact, personal impact, and financial impact of the child's illness. The measures assessed approximate the domains proposed by Jensen et al. (2017) to cover the impact of severe childhood epilepsy on caregivers. The proposed domains are based on the work of internationally represented expert panels and caregiver focus groups. The authors suggest a collective 'life impact' measure to capture a comprehensive assessment of the impact of childhood-onset epilepsy, including caregiver physical and mental health, social function, and financial resources (Jensen et al., 2017).

Measuring the impact childhood epilepsy exert on caregivers is no less challenging when considering the shared experiences of traumas and adversities due to the condition. The following sections will provide an overview of the neurobiology of PTSD, how to assess trauma in children, and the challenges of assessing it in children with epilepsy from a neurodevelopmental perspective.

1.1.4. The neurobiology of post-traumatic stress disorder – a brief overview

The cardinal symptoms of post-traumatic stress disorder are associated with learned reflexive responses, or fear-conditioned responses, and avoidance of being exposed to stimuli that evoke the reflexive responses. The fear-conditioned stress response is a form of classical conditioning in which an instinctive response to an unconditioned stimulus becomes associated with another previously neutral stimulus. Understanding these neuropsychological mechanisms lead to a possible understanding of the underlying brain structures and neural circuitries involved in the changed response mechanisms following exposure to traumatic events.

With the rapid advancements of neuroimaging techniques over the past two decades, the understanding of neural circuitry of PTSD has moved from the exploration of stationary structural changes in the gray matter of brain regions to a network theory of functional connectivity involving large-scale brain networks (Ross & Cisler, 2020). The early investigations of univariate activation patterns of isolated brain regions resulted in a widely accepted general neurocircuitry model of PTSD, including structural alterations of the hippocampus, a hyperactive amygdala, and hypoactive medial prefrontal cortex (mPFC) (Rauch, Shin, & Phelps, 2006) as well as a hyperactive insula (Paulus & Stein, 2006; Simmons, Strigo, Matthews, Paulus, & Stein, 2006). Further advancements in bivariate functional connectivity models support the findings of a hyperresponsive amygdala that mediates hyperarousal symptoms and explains the persistent memory of a traumatic event. Inadequate mPFC response underlies deficits of extinction and the capacity to suppress attention and response to trauma-related stimuli. The decreased hippocampal function contributes to deficits in contextual processing and accompanying explicit memory difficulties (Liberzon & Sripada, 2008; Rauch et al., 2006). Furthermore, the dysregulated signals of bodily awareness arising from the associated rostral anterior insula and mPFC are hypothesized to engender anxiety, rumination, and avoidance behaviors (Liberzon & Sripada, 2008; Paulus & Stein, 2006; Shin & Liberzon, 2010; Simmons et al., 2006).

Additionally, alterations in the neurochemical systems and dysfunctional regulation of hormones of the hypothalamic-pituitary-adrenal (HPA) axis contribute to the learned reflexive survival responses following exposure to a perceived threat (Jovanovic et al., 2010; Ross et al., 2017; Sherin & Nemeroff, 2011).

Although the classical models of activation patterns and functional connectivity may represent an essential understanding of the foundations of PTSD neural circuitry, the emerging field of large-scale network model studies fail to isolate the classic circuits as consistently altered in PTSD groups (Berg et al., 2020; Ross & Cisler, 2020). The network model theory hypothesizes the involvement of three large-scale brain networks[8] in psychopathology called the *'triple network model'* by Menon (Menon, 2011). The three network includes the default mode network (DMN), the central executive network (CEN), and salience network (SN) (for review see; Akiki, Averill, & Abdallah, 2017). The large-scale network involvement, particularly the DMN, will be discussed in association with epilepsy further below.

The pathogenesis of PTSD may be conceptualized as a fear-conditioning process that impacts predisposed vulnerabilities of any combination of the abovementioned deficiencies, and chronic PTSD might involve progressive deterioration of these deficiencies (Howie, Rijal, & Ressler, 2019; Rauch et al., 2006). In addition, genetic factors and epigenetics are associated with the vulnerabilities of those developing PTSD (Ross et al., 2017), which warrants specific awareness of trauma exposure early in life (McEwen, 2017).

[8] Large-scale brain networks are collections of widespread brain regions showing functional connectivity by statistical analysis of diagnostic imaging.

1.1.5. Childhood trauma in a neurodevelopmental perspective

The neurobiological impact of traumatic stress in childhood is associated with brain development and the mechanisms of how the immature brain integrates information into its structure and function. The typical developing brain undergoes naturally occurring changes in structure and function from early childhood to late life, and experiencing stress is an essential part of healthy development. Adverse events may cause changes that lead to learning, growth, and resilience; however, prolonged traumatic exposure may cause regression, cognitive decline, and vulnerability. Thus, traumatic stress may impair brain architecture with different effects on the growth of specific brain regions or structural/functional networks depending on when a child is exposed to trauma (Weems, Russell, Neill, & McCurdy, 2019).

Shortly, the healthy developing brain continues to evolve after birth. In the first five years of life, there is an overall expansion of brain volume related to development. Both gray matter and white matter structures of the brain grow in the early years; however, from about seven into late teenage years, there is a progressive increase in white matter (myelination) and decrease in gray matter (pruning) while overall brain size stays the same (Bremner, 2006). In postnatal development, an overproduction of synapses[9] occurs that depends mainly on genetic origin. This overabundance of synapses is followed by pruning the uncommitted synapses and eliminating connections to strengthen relevant ones. This process is influenced by experience and adaption to the surrounding environment and may involve epigenetic changes (Casey, Tottenham, Liston, & Durston, 2005).

Individual variations of structural and functional connections due to age and maturation of particular interest are the emotion-processing regions. Emotional well-being and age-appropriate social skills are competencies that provide a vital foundation for socioemotional and cognitive growth

[9] Nerve cell connection points where electrical signals move from one nerve cell to another.

in children, as development essentially happens in social interplay until late childhood (Parker, Rubin, Erath, Wojslawowicz, & Buskirk, 2015).

Naturally occurring changes in amygdala volumes are happening during childhood, and stress may alter the expected developmental trends (Weems, 2017). However, the stress-related changes of the age-related amygdala development may not necessarily be currently pathological (Teicher & Samson, 2016). Instead, the process may have been delayed, accelerated, or prolonged depending on the adaptive value of the change (VanTieghem & Tottenham, 2018).

Even though alterations of the structure and function of the amygdala and adjacent emotion processing regions may not be pathological, the altered neurocognitive functioning following childhood adversities is evident even in the absence of overt psychopathology and may warrant future development of psychopathology (Bick & Nelson, 2016; McCrory, Gerin, & Viding, 2017; Nelson & Jeste, 2008).

Of further interest is the neurobiological changes of stress responsiveness from childhood into adulthood. Stress response presents as neuronal activation in subcortical areas of the brain[10] in childhood and manifests as increased motor activity. Hormonal changes during adolescence are hypothesized to aid in the transition into a predominant involvement of cortical activation[11] that increases cognitive response to stress in adulthood (for an overview, see: Andersen, 2003). In addition, epigenetic changes early in life due to stress exposure have proved to result in long-term alterations of the HPA axis regulation, and thereby affecting the ability to regulate the stress response later in life (Champagne, 2010; Kaufman & Charney, 2001; Ross et al., 2017). However, it is hypothesized that the enhanced vulnerability of the pre-pubertal brain may either consolidate the neurobiological changes due to early-life adversities or represent a window of opportunity to redirect aberrant development back onto a typical trajectory (Andersen, 2003).

[10] Specifically nucleus accumbens and related network distribution.
[11] Prefrontal cortex.

In children with epilepsy, the natural process of neurobiological development is challenged by the nature of the condition itself and its treatment. It is beyond the scope of this thesis to describe the many different etiologies associated with seizure-related conditions in childhood; however, the basic understanding of a seizure being a sudden, uncontrolled electrical disturbance in the brain is essential. Epileptic seizures are disturbances in the brain's neurochemical systems based primarily on structural abnormalities or a genetic disorder (for a complete list of etiology, see; Brodie, Zuberi, Scheffer, & Fisher, 2018; Scheffer et al., 2017).

This innate vulnerably of the epileptic brain may challenge the resilience of the child when faced with adversities. Physical and mental stress are well-known factors that can induce seizures (McKee & Privitera, 2017), and stress sensitivity of seizures in children has shown to be associated with alterations of the stress response (van Campen et al., 2015). Furthermore, functional connectivity studies have provided insight into the association between epileptic networks and networks involved in psychopathology (Xiao, An, & Zhou, 2017); although, shared genetic variances across psychopathology and epilepsy have yet to be proved (Campbell, Cavalleri, & Delanty, 2020).

However, the developmental differences, particularly the innate vulnerability of the epileptic brain, indicate the relevancy of studying trauma assessment in children carefully.

1.1.6. Assessing trauma symptoms in children with epilepsy

The age and developmental stage of a child affect the way the child experience and express trauma symptoms (Scheeringa, Myers, Putnam, & Zeanah, 2012). However, the diagnostic criteria for post-traumatic stress disorder (PTSD) in children and adolescents are comparable to adults'. With the recent updates of the two diagnostic manuals, DSM (DSM-5, 2013) and ICD (ICD-11, 2018), the PTSD diagnosis has undergone significant changes in both manuals. The DSM has broadened the criterion for meeting the PTSD diagnosis, including recognizing secondary traumatization, and the

ICD has narrowed in the definitions for a higher specificity (Stein et al., 2014). These changes have different advantages when assessing and recognizing trauma reactions in children. In addition, the two manuals each have advancements that are particularly relevant when assessing the impact of trauma exposure in children with epilepsy.

PTSD - DSM

To meet the diagnostic criteria of the recently updated DSM-5 PTSD diagnosis (American Psychiatric Association, 2013), a person can either be directly exposed to a traumatic event, witnessing it, learning that a relative was exposed to it, or indirectly by exposure to distressing details of an event, such as repeatedly hearing details about it. The definition of trauma requires exposure to actual or threatened death, serious injury, or sexual violence, and trauma symptoms have to cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. Trauma symptoms are organized into four symptom clusters: re-experience, avoidance, negative alterations in cognitions and mood, and arousal.

To fulfill the criteria of trauma exposure in DSM-IV, a person should have experienced, witnessed, or had been confronted with an event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others. Secondly, the person's response to the traumatic event should involve intense fear, helplessness, or horror. The trauma symptoms are centered around three out of the four clusters in DSM-5: re-experience, avoidance, and arousal symptoms.

The change from DSM-IV to DSM-5 in the exposure criteria opens for indirect exposure to traumatic events through the experience of others. It considers that not all people who develop PTSD had an initial response to the event (Friedman, Resick, Bryant, & Brewin, 2011).

Thus, the DSM-5 recognizes indirect trauma exposure, acknowledging the risk of secondary traumatization (Figley, 1995; Motta, 2015). The theory of secondary traumatization states that the

consequences of trauma exposure are not limited to the person who experiences a traumatic event but can also affect close relatives, such as a child (Howard, 2021; Steinberg, 1998). Secondary trauma has been demonstrated in, but is not limited to, children of war veterans (Rosenheck & Nathan, 1985), parents with mental illness (Lombardo & Motta, 2008), and survivors of stalking (Elklit, Gregers, Olsen, & Al, 2019).

The theory explains that a parent can transfer their psychological symptoms to their child directly, in the sense that the child develops the same symptoms, or indirectly, by the child getting affected by his/her parent's moods, behaviors, fears, or narratives, which influences the child's function and development (Schwerdtfeger & Goff, 2007).

A child with epilepsy is exposed to various potentially traumatic events, such as injuries following seizures and frequent hospital visits (Jennum, Pickering, Christensen, Ibsen, & Kjellberg, 2016). Non-generalized seizures where the child experience a loss of control over body parts, speech, visual impressions, or other visible change of normal functioning, may be characterized as traumatic events as a threat of serious injury. The parental exposure to and the child's experiences of different adversities may collectively result in an augmentation of trauma exposure, including possible secondary traumatization of the child as per the exposure definition of DSM-5.

PTSD - ICD

To improve the specificity of the PTSD diagnosis, the ICD criteria for PTSD have changed into fewer symptoms and a more simple structure in ICD-11 released in 2018 (Brewin et al., 2017), contradictory to the expansion of symptoms and symptom clusters in the updated DSM-5. Symptoms of sleep and concentration difficulties have been excluded from the arousal cluster in ICD-11; however, functional impairment has been added as a criterion to be fulfilled to meet the diagnosis of PTSD in concordance with the DSM criterion. The ICD-11 PTSD diagnosis requires exposure to a trauma defined as an extremely threatening or horrific event or series of events. The disorder includes

three symptom clusters: re-experiencing the traumatic event in the present, avoiding traumatic reminders, and a sense of current threat. The re-experiencing and avoidance symptoms refer specifically to the traumatic event, and the disorder is primarily conceptualized as a conditioned fear response.

ICD-11 also introduced a new diagnosis of Complex PTSD (CPTSD) (World Health Organization, 2019). The diagnosis is proposed to typically result from prolonged, chronic exposure to traumatic events, although the CPTSD diagnostic criteria do not require a repeated experience of trauma. However, the diagnosis of CPTSD in children and adolescents is likely to be infrequent following single-incident trauma events (Elliott et al., 2021). To meet the criteria of CPTSD, full PTSD diagnostic criteria should be met in addition to three additional symptom clusters that reflect disturbances in self-organization (DSO symptoms): affect dysregulation, negative self-concept, and interpersonal difficulties.

There is some evidence that ICD-11 may reduce diagnostic rates in children and adolescents relative to ICD-10 (Elliott et al., 2021; Sachser & Goldbeck, 2016) and relative to DSM-5 in preschool children (1–6 years old) (Vasileva, Haag, Landolt, & Petermann, 2018). Although the reduced identification of PTSD in ICD-11 relative to DSM-IV and DSM-5 are demonstrated in some studies in young trauma-exposed adults (Hafstad, Thoresen, Wentzel-Larsen, Maercker, & Dyb, 2017; O'Donnell et al., 2014), other cohort studies find the exact prevalence of PTSD across the DSM-IV/5 and ICD-11 when measuring on the general population (Stein et al., 2014).

The specificity of the ICD-11 PTSD diagnosis is particularly relevant to explore in children and adolescents, as the behavioral symptoms that were excluded (sleep and concentration difficulties) are indicators of PTSD that are more readily identifiable by parents compared to children's cognitive symptoms, which are more difficult to evaluate by observers (Smith, Dalgleish, & Meiser-Stedman, 2019). However, the symptoms are also frequently occurring sequelae to epilepsy in children. Thus,

the cluster of symptoms might better differentiate between specific trauma symptoms and potential epilepsy sequelae by excluding these symptoms from the arousal cluster.

The following description of trauma symptoms specific to age will review the three clusters of trauma symptoms included across all versions of PTSD diagnostic criteria, re-experience, avoidance, and arousal/sense of current threat. Although not specified in ICD-11, descriptions of developmental differences in symptom expression for children are included in DSM-5. Furthermore, DSM-5 includes a separate set of developmentally sensitive criteria with three symptom groups for children under seven (American Psychiatric Association, 2013).

Early childhood (Age 0–6)

The challenge of assessing trauma symptoms in young children is the absence of or limited language and communications skills. Thus, the assessment can primarily be based on behavior and emotional expressions in certain situations (Gaensbauer, 1995). For example, symptoms of re-experiencing trauma may be exposed via the re-enacting of trauma themes in play (Kerig, Fedorowicz, Brown, & Warren, 2000) or by flashbacks and nightmares for the children that have the language to express these experiences, or intense emotional or physical reactions to reminders of the event.

Dissociative episodes in which the child freezes and becomes unresponsive may be a symptom of avoidant coping behavior (Kerig et al., 2000). Furthermore, subtle or pronounced avoidant symptoms can be observed in withdrawal from social interactions, limited engagement or regression, and denial when conversations entail detailing reminders of the trauma (De Young, Kenardy, & Cobham, 2011).

Arousal is often observed by increased irritability, fussiness and activity level, sleep disturbances, temper tantrums, poor concentration, and hypervigilance (Kerig et al., 2000).

Many of the symptoms, especially the avoidant and arousal clusters, are frequently occurring in children with epilepsy, although framed as behavioral difficulties and psychiatric comorbidity associated with the etiology of epilepsy (Besag et al., 2016; Besag, 2002; Reilly et al., 2013). Thus, assessing these symptoms in young childhood entails challenges when the child cannot express eventual associations between behaviors and specific traumatic experiences.

Schoolchildren (Age 7–11)

When acquiring language and communication skills, schoolchildren can express fears and often re-experience details of a traumatic event via intrusive sounds or images. Trauma-related games and recurrent revenge or rescue fantasies can be observed. The age group can express the experience of symptoms such as trauma-specific fears, somatic complaints, and nightmares, and develop new fears, and be experienced with increased reactivity (Kerig et al., 2000). Avoidance symptoms can be seen as phobic behavior, sadness, truancy, loneliness, guilt, withdrawal from peers and play, and a feeling of having a limited future. Dissociative episodes are similar to those experienced by preschoolers (De Young et al., 2011; Kerig et al., 2000).

Increased arousal can show in a range of symptoms, such as difficulties falling asleep, diminished academic aptitude, oppositional defiance, obsession with trauma details, and an exaggerated startle response (Kerig et al., 2000). In addition, the traumatic experience can diminish the child's capacity to express affection, and the child's risk behavior may increase beyond their age-appropriate capabilities (Pynoos, Steinberg, & Goenjian, 1996).

Once again, the symptoms do not distinguish considerably from symptoms commonly observed in children with epilepsy. However, the re-experiencing symptoms are specifically trauma-related in their content. Therefore, they can only be measured if the child can express the content and thus may warrant a difference between epilepsy-related sequelae and trauma-related behavior.

Adolescents (Age 12–18)

Analogous to the re-experience symptoms of schoolchildren, adolescents report symptoms of recurrent revenge and rescue fantasies, flashbacks, nightmares, trauma-specific and mundane fears, and somatic pain. Arousal symptoms such as insomnia or the opposite; withdrawal into heavy sleep, anger, and aggression are commonly disclosed (Kerig et al., 2000). Social withdrawal and isolation or acting out may be a consequence of the inability to cope with routine and daily life (Margolin & Vickerman, 2007). Alterations in arousal and mood may also be seen as a higher risk of engaging in risky or destructive behaviors, e.g., substance abuse, eating disorders, truancy, and violence (Margolin & Vickerman, 2007; Pynoos et al., 2009).

This chapter has provided an insight into the complexity of understanding the family impact of complex childhood epilepsy and the challenges of quantifying this issue. It has further provided a perspective of childhood trauma in childhood epilepsy and why this may be a crucial issue to consider when assessing the condition's impact on the affected child and its parents.

The following chapters will present the PhD project and expand further on these issues in the discussion.

2. Rationale and aims

The overall aim of this PhD project is to understand the support needs of families living with complex childhood epilepsy to provide better comprehensive care and target interventions in clinical settings that help parents retain or regain their resources.

The rationale behind this aim is that resourceful parents can provide the needed care to their affected child. Moreover, epilepsy occurring early in life often leads to multiple adversities during childhood, and caregivers need resources to handle these events and maintain everyday life with a mental surplus.

Additionally, with the knowledge of the innate vulnerability of the epileptic brain and how adversities in childhood affect the normal development of the immature brain, the development of psychopathology at some point in people with childhood-onset complex epilepsy seems inevitable. However, although the prevalence of psychopathology in children with epilepsy is high, not all children have comorbid mental difficulties. Thus, some children may have developed a resilience towards developing psychopathology, and contextual resources could mitigate the consequences of the adversities.

Therefore, with a better understanding of the neurobiological mechanisms associated with childhood adversities, the differentiated neuronal networks engaged in different types of epilepsy, and when the developing brain is sensitive to change, treatment options can be better targeted for the entire family to possible prevent aggravating development of distress and psychopathology. Moreover, timely intervention in this perspective may eventually even have an impact on the condition itself.

These hypothesized associations formed the basis for this current work. However, with limited knowledge about trauma response prevalence in children with epilepsy and contextual resources in

their caregivers, developing directed intervention methods did not seem fully achievable before the scope of these issues was addressed.

Thus, the study addresses three research questions to build the foundation from which intervention can be targeted; 1) the prevalence and associations of parental stress and psychopathology, 2) the prevalence of child trauma symptoms and psychopathology, and 3) the impact on the family as a system when a child has complex epilepsy.

3. Methods

The project is a cross-sectional study based on parental questionnaires and developmental sensitive assessment tools for children. Data collection took place at the neuropediatric department at the Danish Epilepsy Center Filadelfia for one year from January 1st through December 31st, 2017. Filadelfia is the only tertiary epilepsy hospital in Denmark, and children submitted to hospitalization have a severity of epilepsy that demands specialist care.

3.1.Participants

Parents and their children aged 0-18 years were approached for participation in the study when hospitalized with their child at the neuropediatric department. They were informed about the survey by the hospital staff on the first day of their admission. Parental questionnaires were handed out on paper with an envelope for anonymous return. Participants signed informed consent, and data handling guidelines from the Danish Data Protection Agency were followed. Trained clinical staff visited the families during their stay to ensure the families had received the survey and to be of disposal for any questions. Parents of children having EEG monitoring for consecutive days and nights were handed the survey to fill out when convenient without any further visit from clinic staff

due to the vulnerability of the situation. Parents of children with short-term stays under 24 hours were only approached if their schedule during their stay permitted an introduction to the survey.

During the 12 months of data collection, 437 children were hospitalized at least once. Caregivers who were not native Danish speakers and non-biological parents were excluded. In total, parents of 287 children were informed about the survey and invited to participate.

Parents were asked for demographic information, including gender and age (caregiver and child), caregiver education, job situation, and marital status. The caregiver further provided diagnostic information concerning the child. Epilepsy-related factors included the type of epilepsy, type and frequency of seizures, the child's age at seizure onset, years with epilepsy, and anti-epileptic drugs (AED). Further, child psychiatric disorders, age at school entry, and current school or day-care facility were asked for as indicators of the child's level of everyday function.

A pediatrician reviewed the diagnostic information regarding epilepsy diagnosis and type of seizures to categorize analyses matching the diagnostic criteria of the International League Against Epilepsy (ILAE) (Scheffer et al., 2017).

Children above the age of six who were attending school activities at the hospital during their hospitalization or otherwise were evaluated to read and write or understand verbal given messages sufficiently were invited to participate in the child and adolescent PTSD survey. Parents of children below the age of seven were further asked to complete an interview about their child if they stated that the child could communicate with the parent.

The following sections will describe the questionnaires and assessment tools used to assess the three research questions. The specific use of each assessment across the studies will be outlined in the result section.

3.2.Parental questionnaires

Seven different questionnaires concerned the participating caregivers.

Parental psychopathology

Two unidimensional subscales of the Hopkins Symptom Checklist-90 (SCL-90) (Derogatis, Lipman, & Covi, 1973) were used to measure the level of depression (HAM-D6) and anxiety (SCL-ASS8) symptomatology. The SCL-90 is a well-established patient-reported questionnaire for measuring psychological distress or the degree of affective distress, targeting nine different psychopathological issues. The HAM-D6 and SCL-ASS8 include core measures of depression and anxiety, respectively, and have unidimensional properties (Bech, Bille, Moller, Hellstrom, & Ostergaard, 2014).

The items on the subscales are rated on a five-point Likert scale ranging from 0 (not at all) to 4 (extremely). The questions relate to emotions and behaviors the past week. The scales include six (HAM-D6) and eight (SCL-ASS8) questions, respectively.

A score between 12 and 15 (both included) meets the criterion of moderate depression, and scores of 16 and above meet the criterion of severe depression. For the anxiety scale, a score of 14 and above indicate anxiety symptomatology.

The subscales of the SCL-90 are validated in a Danish community sample of 1153 adults (Olsen, Mortensen, & Bech, 2004) with acceptable internal validity for the non-psychotic subscales.

Post-traumatic stress disorder (PTSD) and the new distinct diagnosis introduced with the ICD-11 manual, complex PTSD (CPTSD), were assessed using the International Trauma Questionnaire (ITQ) (Cloitre, Garvert, Brewin, Bryant, & Maercker, 2013; Hyland, Shevlin, Brewin, et al., 2017; Hyland, Shevlin, Elklit, et al., 2017).

The scale has been under substantial revisions since the initial version of the ITQ, and the final version is a 12 item self-report measure for the assessment of the ICD-11 criterion for PTSD and complex PTSD (CPTSD) (Cloitre et al., 2018). The ITQ includes six items to assess symptoms of PTSD (three clusters of symptoms) and six items that assess symptoms of disturbances in self-organization (DSO) (likewise three clusters of symptoms). Each cluster includes two items. The scale includes additional three items assessing functional impairment related to PTSD and DSO separately. Items are scored on a five-point Likert scale from 0 ('Not at all') to 4 ('Extremely'). Symptoms are considered endorsed with scores of two ('Moderately') or more.

For a probable diagnosis of PTSD, one symptom is required in each of the re-experiencing, avoidance, and sense of threat clusters and a score of two or more on one of the associated functional impairment items. A subthreshold of PTSD (sub-clinical level) requires two out of three cluster symptoms present. For a probable diagnosis of CPTSD, additionally to a diagnosis of PTSD, one symptom is required in each of the clusters for affective dysregulation, negative self-concept, and disturbed relationships. Similarly, one of the three questions assessing functional impairment related to DSO should have a score of two or more.

The construct validity of a Danish translated final version has recently been tested in five clinical samples and was found supported (Vang et al., 2021).

As data collection and analyses of our study were conducted before the final version of the ITQ was published, items consistent with a revised version containing seven items for PTSD analyses and 17 items for the CPTSD analyses have been used in PhD paper I. However, analyses using the 12-item final version have been included in the Erratum, Appendix D.

Items assessing functional impairment were not included; hence, results are referred to as symptoms of PTSD and CPTSD in the PhD paper I.

For PTSD symptoms in caregivers in PhD paper II, the 6-item final version has been used.

Parental stress

The well-established 10-item Perceived Stress Scale (PSS-10) (Cohen, Kamarck, & Mermelstein, 1983) was used to measure the caregiver's level of perceived stress. The self-reported questionnaire evaluates the degree to which individuals believe their lives have been unpredictable, uncontrollable, and overloaded during the previous month in general. The scale is a five-point Likers scale from 0 (‘Never’) to 4 (‘Very often’), where a higher score resembles higher levels of perceived stress. The 10-item scale has proved superior to the original 14-item scale and has shown acceptable psychometric properties across various cultures and countries (Lee, 2012; Liu et al., 2020).

Family impact

The impact of epilepsy on the family was measured by the Impact on Family Scale (IFS) (Stein & Riessman, 1980). Scores are measured on a four-point Likert scale from 1 (‘Absolutely agree’) to 4 (‘Absolutely disagree’). Thus, a low total score defines a high impact.

The aim of the original 24-item scale was explicitly to assess the impact of pediatric chronic illness on the family by four different measures: personal strain, familial/social impact, financial impact, and mastery. A revised IFS scale with 15 out of the original 24 items was later recommended to measure a single impact factor, showing good to excellent psychometric properties (Stein & Jessop, 2003; Williams, Piamjariyakul, Williams, Bruggeman, & Cabanela, 2006). The construct validity and reliability have recently been tested on 219 parents of children with epilepsy and was found to be a practicable, reliable, and valid tool to assess the impact of childhood epilepsy on family life in research and clinical practice (Dehn et al., 2014).

The 15-item scale was used as a single factor measure of the general impact on the family in this study. In addition, further sub-analyses were performed on two of the original scales—personal strain and familial/social impact—due to the qualitative nature of the questions in these two scales.

Parental resources

The Multi-dimensional Scale of Perceived Social Support (MSPSS) (Zimet, Dahlem, Zimet, & Farley, 1988) was used to measure external resources in caregivers. The MSPSS is a 12-item measure of perceived adequacy of social support from three sources: family, friends, and a significant other. The seven-point Likert scale goes from 1 ('Highly disagree') to 7 ('Highly agree'), and higher scores equal higher levels of support. A total scale across the three sources was used in this study.

The subscales and the total scale have good internal reliability with Cronbach's alpha (α) levels between 0.81 and 0.94 (Zimet, Powell, Farley, Werkman, & Berkoff, 1990).

The Visual Analogue Scale of Self-control (VAS-SC) (Bandura, 1997; Rosenberg, 1965; Rotter, 1966) was used to measure a psychological feature of parental resources. The VAS-SC consists of a 10-centimeter line anchored at each end by two opposing statements related to the experience of the sense of control (self-control). At the high end of the scale (to the right) is the statement: 'I do not feel that I am in control of what direction my life takes' (low level of self-control). On the opposite end (to the left) is the statement: 'Usually, I control what is happening to me'. Hence, the higher the score, the lower sense of control.

The VAS scale measures have reliable psychometric properties compared to Likert-scale measures (Hasson & Arnetz; Sung & Wu, 2018).

Parental coping

The Coping Style Questionnaire (CSQ) (Roger, Jarvis, & Najarian, 1993) is a 37-item, four-point Likert scale measure of parental coping styles. The score goes from 1 ('Never') to 4 ('Always'), with a higher score representing a more pronounced response style. The questions relate to how a person typically reacts to significant stressors or in stressful situations. Thus, the scale measures a higher-order coping response style rather than practical behavioral or cognitive coping strategies (Brown & Bond, 2019).

The questionnaire distinguishes between four different coping styles, two adaptive and two maladaptive, each with acceptable internal consistency of the scales (Cronbach's alpha (α)): rational coping (RATCOP; α = 0.85) and detached coping (DETCOP; α = 0.90) (both adaptive) and emotional coping (EMCOP; α = 0.74) and avoidance coping (AVCOP; α = 0.69) (maladaptive) (Elklit, 1996).

3.3. Child assessments

Parents completed two questionnaires regarding their child's level of functioning. The Strength and Difficulties Questionnaire Parent Form (SDQ-P) (Goodman, 1997) was used to measure the child's level of behavioral difficulties. The SDQ is a widely used and reviewed 25-item, three-point Likert scale questionnaire (Goodman, 2001; Kersten et al., 2016) with strong psychometric properties (Stone, Otten, Engels, Vermulst, & Janssens, 2010). It is validated for a Danish population (Arnfred et al., 2019). It includes five subscales: Emotional Symptoms, Conduct Problems, Hyperactivity, Peer Problems, and Prosocial Behavior. The first four scales are summed to a total score as a measure of child behavioral difficulties. Thus, a higher total score approximates higher levels of behavioral difficulties.

The Comprehensive Executive Function Inventory (CEFI) (Naglieri & Goldstein, 2014) is a behavior rating scale of the strengths and weaknesses of executive functioning. The parents for children above the age of 6 years complete the scale. The rating scale contains 100 items rated on a 6-point scale, with 90 items covering nine different executive skills and a total score. The scores are converted to scaled scores with a mean of 100 and SD of 15. The total score was used as a measure of the child's level of cognitive functioning. The inventory has strong psychometric properties and is valued within research and clinical practice (Fenwick & McCrimmon, 2015).

Child psychopathology

To measure child PTSD and psychopathology in children below six years, parents were interviewed with The Diagnostic Infant and Preschool Assessment (DIPA) (Scheeringa & Haslett, 2010). The assessment tool is a structured clinical interview administered to the caregiver of children under the age of seven. The interview consists of 517 questions used to identify symptoms across 13 different psychiatric disorders. The PTSD section of the interview lists 11 possible traumatic events, and one question is open for other events than the listed, which the parent answer on behalf of the child. If the child had been exposed to more than one event, the parent would have to rate the worst. The parent then has to answer 55 consecutive questions related to re-experiencing, avoidance, and arousal behavior/reactions associated with the worst event. Lastly, the degree of functional impairment due to the reactions and behaviors is assessed.

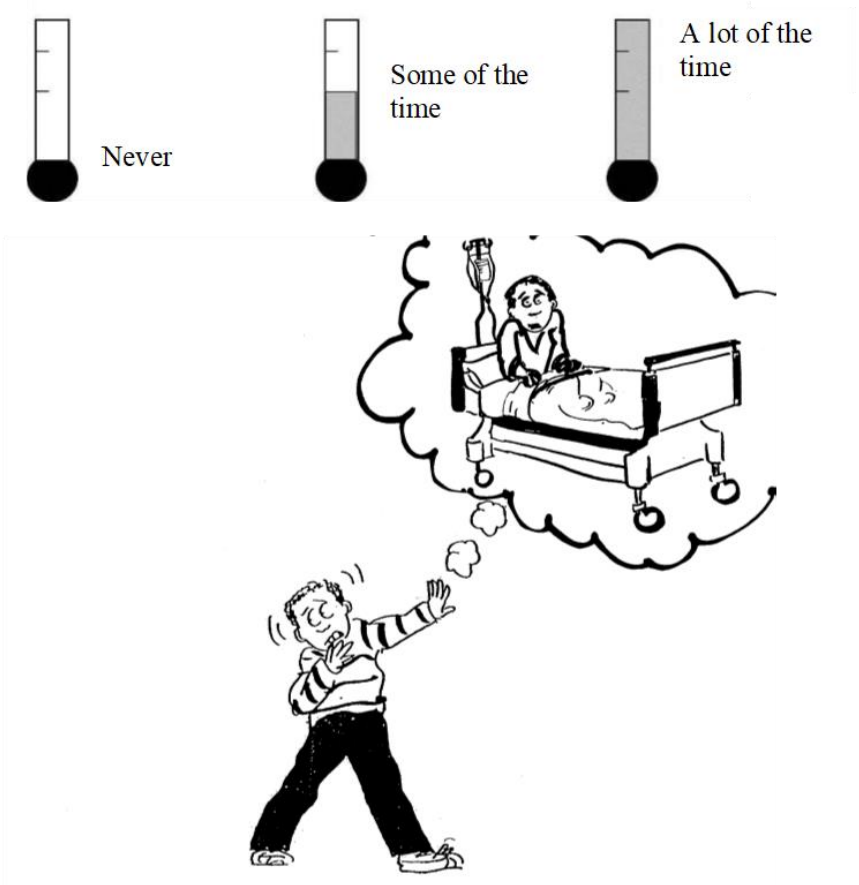
The criterion of a PTSD diagnosis is met if the child has one symptom of re-experiencing, three avoidance symptoms, two arousal symptoms, and one functional impairment symptom. The interview is validated across different countries and has proved to be a sensitive tool when measuring psychiatric disorders in preschool children (Gigengack et al., 2020; Løkkegaard, Elmose, & Elklit, 2019; Pynoos et al., 2009). A validated Danish version of DIPA (Løkkegaard et al., 2019) based on the DSM-IV (Association, 2000) was used in this study.

To measure symptoms of PTSD in children above six years of age, Darryl's cartoon test was administered to children between the age of six and 12 years.

The Darryl cartoon test is a screening tool used to identify and measure PTSD symptoms in children and adolescents (Geller et al., 2007; Neugebauer et al., 1999). The test consists of 23 cartoons of a pre-adolescent boy named Darryl, accompanied by three empty, half-full, and full thermometers. A text about the psychological response specific to an illness-related experience is read to the child. The experience is illustrated in the feelings of Darryl depicted in the cartoon. The child has to identify

if he or she feels the same way as Darryl and circle the thermometer that best matches the child's feelings.

Nineteen cartoons are associated with trauma symptoms; seven related to re-experiencing, seven related to avoidance, and five related to arousal. The symptom criteria are met if the child appoints a half-full or full thermometer resembling an item-score of one or two, respectively.



'Darryl has tried to avoid to think or talk about his illness ever since he became ill.

How often do you try not to think or talk about it like Darryl?'

The Darryl's cartoon © Copyright Dr. Richard Neugebauer, Ph.D. Professor Ask Elklit (aelklit@health.sdu.dk).
Pictures from The National Center of Psychotraumatology. Brought with permission.

The specific cluster criterion is met for one endorsed re-experiencing symptom, three endorsed avoidance symptoms, and two endorsed arousal symptoms. If all three cluster criteria are met, the

criterion of PTSD is fulfilled. A subthreshold of PTSD (sub-clinical level of PTSD) requires two out of three cluster criteria to be met.

The Darryl cartoon test assesses PTSD symptoms developmentally appropriately (Geller et al., 2007). In addition, it is validated for a Danish population with good internal consistency for the overall scale ($\alpha = 0.88$) (Schandorph Løkkegaard, Rønholt, Karsberg, & Elklit, 2017). Since the test has yet to be systematically validated for the DSM-5, the DSM-IV is referenced in the current study.

Adolescents between the ages of 13 and 18 were asked to answer The International Trauma Questionnaire (ITQ) equivalent to the one their parents answered to measure symptoms of PTSD. A trained clinician was at the disposal if the adolescent needed help to fill out the questionnaire. Items consistent with the final version of the ITQ were used to analyze adolescent PTSD symptoms, although measures of CPTSD were not included for the adolescents.

An ITQ version for children and adolescents with adapted language use has been proposed (ITQ-CA) (Haselgruber, Sölva, & Lueger-Schuster, 2020); however, the version has yet to be validated in Denmark. Nevertheless, the construct validity of the current ITQ scale has been validated in child and adolescent populations aged 10-18 years (Haselgruber, Solva, & Lueger-Schuster, 2020; Kazlauskas et al., 2020).

The following section will briefly describe the general handling of data. This section will not describe the statistical analyses used to answer each research question to avoid content repetition. Instead, each of the three PhD papers will walk through the analyses in detail.

3.4. Data handling and analyses

Data were collected on paper and handled twice in the process of digitalization. Quantitative statistics were analyzed by syntax using IBM SPSS version 24 (IBM, 2016). First, all questionnaire variables were screened for accuracy (min. and max statistics) and missing data. Second, little's

MCAR test was performed, and missing values up to 20 % at item or case level were imputed using the expectation-maximization (EM) method. This method was run for each subdomain of questionnaire scales if the scale included more than one total measure. Manual described algorithms were used to calculate cut-off scores for psychopathology measures (HAM-D6, SCL-ASS8, ITQ, THOMAS, and DIPA) equivalent to the criteria definitions stated above.

All continuous scales were assessed for residual normality, linearity, and homoscedasticity assumptions and were transformed if necessary. Transferred scales are mentioned as such in the text, tables and figures were relevant.

4. Results

The main results of each research question will be described in this section. For detailed quantitative results, see the designated PhD paper in the appendices.

Overall, the survey was completed by 162 caregivers (of whom 125 were mothers and 37 fathers) aged 27-60 years (mean 39.8 years, SD 6.7). Both parents of 22 children participated in the survey; thus, the survey encountered 140 children with complex epilepsy, giving a response rate of 49 %. The children had a mean age of 8.9 years (0-18 years; SD 4.6) and a mean duration of epilepsy of 4.03 years (SD 3.72). (Table I).

Forty-seven percent of the children attended special needs classes, and 38 % had a deferred school entry, indicating some degree of delayed development. Seventy-two percent of the parents cohabited with the child's other parent, and 65 % had a part-time or full-time job. Mothers were more often unemployed than fathers (38% vs. 11%, $p<0.01$), and two-thirds of the unemployed mothers (24 % of the total) were compensated full-time for loss of earnings due to illness severity, compared to 3 % of fathers.

Due to restrictions in the European General Data Protection Regulation (GDPR), collecting personal data on parents or children without consent was not permitted. However, the age and gender of the children hospitalized during the data collection period were assessable from general hospital admission registers. Children of parents who declined to participate in the survey (n = 147) had a mean age of 9.3 (0-18 years; SD 4.4), and 43 % were girls. Available non-responders were asked for the reason behind their decline to participate in the survey. Some responses from those who gave a justified answer have been written in the limitation section below.

Table I: Group Characteristics

Child	
Number of patients (girls %)	140 (46)
Age, *M* (SD)	8.9 (4.56)
Years with epilepsy, *M* (SD)	4.0 (3.72)
Epileptic diagnosis, *n* (%)	
Epileptic encephalopathy	26 (19)
Focal/multifocal epilepsy	73 (52)
Idiopathic generalized epilepsy	20 (15)
ESES	21 (14)
Seizure frequency, *n* (%)	
Seizure-free	37 (30)
Daily seizures	42 (34)
Weekly or less often seizures	44 (36)
Attended school later than expected, *n* (%)	40 (38)*
School for children with special needs, *n* (%)	49 (47)*
Psychiatric diagnosis, *n* (%)	16 (15)*
Caregiver	
Number of parents (women %)	162 (77)
Civil status, *n* (%)	
Both parents living together	117 (72)
Work situation, *n* (%)	
Employed	106 (65)
Compensated for loss of earnings	29 (18)

* *n*=105, age > 5. M = mean. SD = standard deviation. n = number.
ESES = Electrical status epilepticus during slow-wave sleep.

4.1. Caregiver impact (PhD paper I)

To answer research question one concerning the prevalence and associations of parental stress and psychopathology, we analyzed responses of the HAM-D6, SCL-ASS8, ITQ, and PSS-10 scales. In addition, the MSPSS were used to assess caregiver resources related to social support, and the SDQ-P scale was used to indicate the level of child sequelae as expressed in child behavioral difficulties.

PTSD, C-PTSD, depression, and anxiety

The response rate for the ITQ questionnaire was 81 % (n=132). Of this group, 26 (20 %)[12] gave answers equivalent to the symptomatology of a PTSD diagnosis. An additional 25 (19 %) had sub-clinical symptoms as they reached cut-off scores on two out of three symptom clusters. One-third of those with PTSD symptomatology also exhibited symptoms of CPTSD (7 %). Seventy-three percent of caregivers with PTSD symptomatology showed co-occurring symptoms of moderate (26 %) to severe (47 %) depression.

The prevalence of depressive symptomatology in the total sample was 35 %, of whom 16 % had symptoms of severe depression and 19 % of moderate depression. Anxiety symptoms were found in 15 % of parents and half of the parents with a co-existing PTSD (53 %). Hence, in total, 44 % of the included parents showed symptoms of psychopathology by fulfilling the criteria for one or more diagnoses. An additional 11 % of the parents showed symptoms of sub-clinical PTSD alone.

Bivariate analyses revealed that psychopathology was significantly associated with employment status, educational level, and child behavioral difficulties. Caregivers without current employment and less than five years of education after primary school displayed a higher level of psychopathology than employed parents and parents with higher educational levels. Parents with

[12] See the corrected prevalence of PTSD, CPTSD and concurrent depression and anxiety in Appendix D: Erratum.

symptoms of psychopathology rated Child behavior difficulties significantly higher than a parent without symptoms. There were no parental gender differences related to psychopathology, and no other child or epilepsy-related factors were individually significantly associated with PTSD, depression, or anxiety. Statistical non-significant results are described further in PhD paper I.

Perceived stress

Bivariate analyses showed higher levels of stress in parents without current employment. Higher levels of social support were associated with lower stress levels, and lower levels of sense of control over life circumstances were associated with higher stress levels. The younger the child's age and the higher the level of child behavior difficulties, the higher level of perceived stress. However, only social support, child behavior difficulties, and control of own situation remained significant when controlling for the remaining variables.

4.2. Child trauma symptoms (PhD paper II)

Research question two regarding the prevalence of child trauma symptoms and psychopathology were assessed by the DIPA interview (0-5 yrs., *n* = 16), THOMAS assessment (6-12 yrs., *n* = 29), and the ITQ questionnaire (13-18 yrs., *n* = 5). The SDQ-P scale was used to assess child behavioral difficulties, and the CEFI questionnaire was used to assess a proxy measure of child cognitive functioning. Parental measures were assessed as in PhD paper I.

Children above the age of 6 years who were evaluated to read and write or understand verbal messages sufficiently to answer the questionnaires were eligible to participate in the child and adolescent PTSD survey. In addition, parents of children below six years were asked to complete the DIPA interview if the parent stated that the child could communicate with the parent. In total, a subsample of 50 children and caregivers were included in the study about child PTSD

symptomatology. The remaining 90 parent-child dyads were included as a comparison group of child and parent characteristics.

The fifty included children had a mean age of 10.3 years (0-18 years; SD 2.8) and a mean duration of epilepsy of 4.2 years (SD 3.4). Data on the non-included children (n = 90) are described in further detail in PhD paper II for comparison.

Symptoms of post-traumatic stress disorder (PTSD)

The overall prevalence of PTSD symptomatology across the three age groups was 22%. The prevalence was increasing with age, with 6% in preschoolers (0-5 yrs.), 28% in schoolchildren (6-12 yrs.), and 40% in adolescents (13-18 yrs.). Additionally, sub-clinical PTSD symptoms in schoolchildren and adolescents were present in 40 % and 41 %, respectively.

The age at which the child was diagnosed with epilepsy was the only significant factor associated with PTSD symptomatology. Children with PTSD symptoms had a later onset of epilepsy (mean age 7.4 years) than children with no symptoms. No other child or parent-related variables were significantly associated with symptoms of PTSD.

Table II displays the differences between children with and without symptoms of PTSD. Of note is that children with PTSD symptoms had a level of executive functioning within the normal range, whereas children with no symptoms had a level below the normal range. On the contrary, children with PTSD symptoms had more behavioral difficulties than children with no symptoms. The total level of behavioral difficulties was elevated compared to Danish norms across all three age groups in children with and without PTSD symptoms. Particularly the hyperactivity score and prosocial behavior were problematic across all three age groups. See PhD paper II, table 6 for details. Furthermore, 40% of children with PTSD symptomatology lived with a parent with symptoms of psychopathology.

Table II. Child and caregiver variables for children with and without PTSD symptoms

	PTSD	No PTSD
Age at diagnosis, *M* (SD)	7.4 (2.8)*	4.2 (3.6)
Years with epilepsy, *M* (SD)	2.3 (2.5)	4.3 (3.3)
Child age, *M* (SD)	9.7 (4.0)	8.9 (3.5)
Executive function, *M* (SD)	86.8 (14.8)	83.5 (11.6)
Behavioral difficulties, *M* (SD)	18.1 (7.9)	14.7 (5.3)
Epilepsy diagnosis		
Epileptic encephalopathy	0%	
Focal/multifocal epilepsy	35%	
Idiopathic generalized epilepsy	10%	
ESES	11%	
Seizure frequency		
Seizure-free	13%	
Daily seizures	6%	
Weekly or less often seizures	42%	
Caregiver psychopathology	40%	
PTSD	10%	
Depression, moderate	27%	
Depression, severe	9%	
Anxiety	18%	
Perceived stress, *M* (SD)	18.9 (8.3)	20.0 (8.5)

*Bivariate analyses demonstrated a significant difference at the $p < 0.05$ level. M = mean. SD = standard deviation. PTSD = post-traumatic stress disorder. ESES = Electrical status epilepticus during slow-wave sleep.

Symptoms of psychopathology in preschool children

In total, 81% of preschool children had symptoms of one or more psychiatric comorbidity. Except for bipolar disorder, symptoms of all other measured psychiatric disorders by the DIPA interview were present in the preschool sample (n = 16). See PhD paper II, Table 3 for overview. Of notice are the prevalence of attention-deficit disorder (38%), hyperactive disorder (31%), specific phobia (25%), and sleep onset disorder (31%). Due to the limited sample size, no further statistics were executed besides prevalence rates.

4.3. Family impact (PhD paper III)

The IFS scale was used to investigate the last research question concerning the impact on the family as a system when a child has complex epilepsy. As the first analyses associated with stress and psychopathology revealed the primary importance of caregiver resources on the impact on caregivers individually, psychological factors were tested as mediating factors for stress and family impact.

Coping responses were included as a psychological factor and measured by the CSQ questionnaire alongside sense-of-control (VAS-SC).

Mediating factors of perceived stress

Bivariate analyses of coping responses concerning parental stress revealed that the two maladaptive coping responses (emotional and avoidant responses) showed a positive association with stress, and adversely, the two adaptive coping responses (rational and detached responses) were negatively related to parental stress. However, only the emotional coping response (EMCOP) was statistically significant when controlling for other variables associated with stress. When testing the coping response in a serial mediation model with self-control and emotional coping as mediating factors between child behavior difficulties and perceived stress, controlling for social support as a confounding factor, both factors mediated the relationship between child difficulties and parental stress. Less self-control was associated with a higher emotional coping response which was associated with higher levels of stress.

The analyses further revealed that social support deceased to be a protective factor for parental stress with lower self-control and higher emotional coping responses.

The impact on family

Adversely to the first study on parental stress and psychopathology, single epilepsy-related factors were associated with the impact on the family. The age at which the child was diagnosed with epilepsy, the nature of the seizures, and child difficulties were significant predictors of the overall impact on family life. Generalized tonic-clonic seizures alone or with other types of seizures were significantly associated with family impact compared to seizure-free children or other types of seizures alone. The younger the child at diagnosis and the more difficulties parents considered their child to have at the time of the survey, the higher impact on the family.

Even when adding parental psychological factors into the analyses, the child factors remained statistically significant. However, mediation analyses showed that self-control and emotional coping mediated the relationship between child behavior difficulties and family impact (Figure III), working the exact mechanisms as for parental stress; less self-control was associated with higher levels of emotional coping response, which was associated with higher impact on the family.

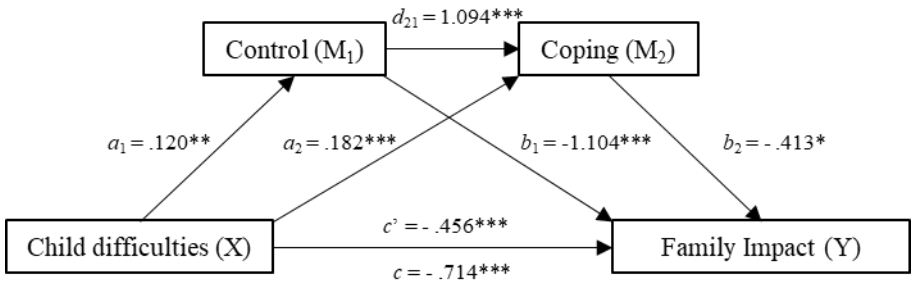


Figure III. Statistical diagram of the serial multiple mediator model for family impact

Specific analyses of the two IFS domains of personal strain and familial/social impact showed that self-control mediated the relationship between child behavior difficulties and impact on both

scales. However, emotional coping response remained significant only in predicting personal strain in association with self-control, so lower self-control and higher levels of emotional coping response were associated with higher personal impact. Only lower self-control was associated with higher familial/social impact.

5. Discussion

The main results of this thesis have demonstrated a high prevalence of stress and psychopathology in caregivers of children with complex epilepsy and that parental individual psychological factors influence the extent to which parents experience stress and family impact. Moreover, trauma symptoms related to the condition are present in children with complex epilepsy, and the prevalence of PTSD symptoms and sub-threshold PTSD symptoms are high in the better functioning children.

The corresponding discussion of the three research questions positioning the results into the existing literature is approached in each of the respective published PhD papers. The following discussion expands on the child trauma perspective and explores the issue within a contextual framework.

The importance of parental care

Although the prevalence of psychopathology in children with epilepsy is high, not all children have comorbid mental difficulties. Thus, some children are more resilient towards developing psychopathology despite the innate vulnerability of the epileptic brain. Therefore, finding out which factors support the constitution of resilience would affect the child's life quality and may even impact the condition itself for some children, in the perspective of stress sensitivity of seizures.

During decades of scientific work, it is well documented that supportive social relationships and engaging relationships with parents can constitute resilience against the development of

psychopathology in children faced with childhood adversities (Gartland et al., 2019; Leung, Chan, & Ho, 2020; Masten & Barnes, 2018). It is further well documented that decreased maternal mental health, and in particular, depression, have an impact on the relationship between mother and child and have consequences for child development related to social competencies and emotional maturity (Bernard-Bonnin, 2004; Cummings & Davies, 1994; Farías-Antúnez, Xavier, & Santos, 2018; Wall-Wieler, Roos, & Gotlib, 2020). With reference to the introductory chapter, age-appropriate social skills are specifically crucial for socioemotional and cognitive growth in children (Parker et al., 2015); hence, early exposure to parental psychopathology may have longer-lasting effects throughout childhood.

The cohort study by Wall-Wieler, Roos, and Gotlib (2020) demonstrates that exposure to maternal depression in the first year of life and between ages four and five has the strongest association with developmental vulnerability at school entry. The emotional and social developmental risks are reflected in negative affect and dysregulated attention and arousal, poor self-control, internalizing and externalizing problems, and difficulties in social interactions with parents and peers (Bernard-Bonnin, 2004). In addition, school-age children and adolescents of depressed parents are at risk for impaired adaptive functioning and psychopathology, according to Bernard-Bonin (2004).

These symptoms commonly occur in children with complex epilepsy, especially those with the earliest onset of epilepsy. As we have only demonstrated an association between child behavioral difficulties and parental stress and psychopathology in our study, the arrow could point in both directions. Hence, child behavior difficulties could lead to decreased parental mental health or the other way around. However, as we demonstrated that parental psychological factors influenced the degree to which parents perceived the association between child behavior difficulties and stress and family impact, there is some evidence for the first statement to be modifiable, and thus may have the ability to change the latter.

Trauma impact in a contextual perspective

Turning to the perspective of trauma impact in children, Weems and colleagues (2019) argue that a person's susceptibility or resilience to the impact of traumatic stress depends on different temporal factors such as the developmental timing of the event, pre-exposure functioning, socioeconomic context, and social support, and genetic susceptibility to environmental influences (Weems et al., 2019).

The developmental timing of trauma exposure concerning the natural neurobiological changes of the brain during childhood has been addressed above. However, as childhood-onset epilepsy include a wide range of syndromes and conditions with onset in all ages and with very different cognitive and developmental trajectories (for an overview, see Helmstaedter & Witt, 2012), the timing of events and the pre-exposure functioning warrant specific awareness when assessing the possible impact of trauma exposure in children with epilepsy. Additionally, in the context of epigenetics, access to responsive and stable caregivers during childhood is considered necessary for normative brain development (Tottenham, 2014). Thus, with a high prevalence of parental psychopathology, the contextual factors affecting the susceptibility for the impact of trauma exposure in children with epilepsy seem challenged altogether.

The bi-directionality of epilepsy and psychopathology

Despite the hesitant approach by Berg and colleagues (2017) to a proposed bi-directionality between epilepsy and psychopathology, recent advancements in neuroimaging techniques support a certain association, although the complex bi-directional interplay is still not well understood (Goodman & Szaflarski, 2021). However, the emerging understanding and acceptance of epilepsy as a network disorder synergizes well with Menon's theorized 'triple network model' of

psychopathology (2011). In particular, the default mode network (DMN)[13] has been a subject for attention in specifically temporal lobe epilepsy (TLE) (Goodman & Szaflarski, 2021; Mohan et al., 2016) and psychopathology (Akiki et al., 2017; Patriat, Birn, Keding, & Herringa, 2016), concerning changes in functional connectivity of regions within the DMN.

Studies of psychopathology in children with TLE demonstrate an exceptionally high prevalence of psychiatric comorbidity, of which depression symptoms are found in up to 84 % of children and adolescents with TLE (McLellan et al., 2005; Pereira & Valente, 2013). The Pereira and Valente (2013) study showed that the severity of depression was not correlated with child- or condition-specific factors. A measure of global functional impairment was elevated for the group but not related to the child- or condition-specific factors. The authors argue that the results contradict the idea of a cause–consequence relationship, referring to the missing association between the severity of condition-specific factors and the severity of depression symptoms. However, from a network perspective, the results might indicate the exact opposite. The distinguished high levels of psychopathology in children with temporal lobe epilepsy and elevated levels of global functional impairment indicate a more general impact of emotion-related networks of the brain-specific to the DMN (Cheng et al., 2018; Schraegle, Nussbaum, & Titus, 2018; Zanão, Lopes, de Campos, Yasuda, & Cendes, 2021).

A recent review by Reilly and colleagues (2019) reviewing the behavioral and emotional functioning outcome after pediatric epilepsy surgery demonstrates some evidence of improvement in emotional and behavioral functioning after epilepsy surgery related to a better seizure outcome. Although the authors emphasize that the outcome scores are confined to parent-reported screening measures of emotional and behavioral symptoms and not clinical diagnoses (Reilly et al., 2019), the

[13] The DMN includes brain regions with high degrees of functional connectivity and is active in the brain at rest, but becomes deactivated when task performance is initiated. Brain areas included in the DMN are the precuneus/posterior cingulate cortex (PCC), medial prefrontal cortex (mPFC), and medial, lateral, and inferior parietal cortex.

findings indicate that when removing the hearth of the condition, global patterns of functionality better objectively seen.

One thing not discussed so far is which factors may trigger behavioral difficulties and psychopathology in children with epilepsy, except for the concept of secondary traumatization. Better functioning children may have the ability to reflect upon their situation, which is a plausible explanation for the development of psychopathology. However, children younger of age and children with complex epilepsy and impaired cognitive functioning may not have the ability to do so as outlined in the introductory chapter. Furthermore, seizures most often involve impaired consciousness, which leaves the child with no constituted memory of what happened during the seizure. Thus, the dominant experience of enduring seizures and living with childhood epilepsy is how the surroundings handle seizures, treatments, and everyday life.

While the innate vulnerability of the epileptic brain cannot be changed, only supported in the context of epigenetics, contextual factors can be modified with the proper knowledge of what needs to be changed or timely supported.

5.1. General methodological considerations

The research project's methodological choice as a self-report survey of parental psychopathology, stress, and family impact may have resulted in less accurate results than if these aspects were assessed through clinical interviews by trained clinicians. However, the applied questionnaires are widely used in the scientific literature across various research fields and have acceptable psychometrically properties as self-report measures.

Furthermore, the parent-proxy measure of child behavior difficulties and executive functioning have its limits as outlined above; however, as a majority of the children included in the study did not

have a functional level sufficient enough to complete self-report measures, the parent completed measure were the best option possible to measure child behavior and cognitive function.

As outlined in the introductory chapter, one measurement tool missing is a globally accepted standard tool for measuring the severity of childhood epilepsy. Such a tool would be beneficial for comparing results across studies and potentially be a valuable tool for clinical work and assessing the support needs of families living with complex childhood epilepsy. Additionally, a globally accepted questionnaire targeting the impact of epilepsy on the family, as proposed by Jensen and colleagues (2017), would have its benefits in research and clinical practices.

Including a relatively broad spectrum of childhood-onset epilepsies and framing it as complex childhood epilepsy demands some considerations. The choice of the name of the group we have studied has been discussed; however, the generalizability of the results may be challenged by the lack of a more specific description of the group. However, as the group is representative of the children and families we encounter at the Danish Epilepsy Center, we have gained a sound foundation to target the intervention-aimed work that will follow this study. Furthermore, the methodological approach is readily reproducible in other tertiary centers across countries and cultures due to the widely used and accepted measurement tools used in the study.

Finally, measuring trauma response symptoms and PTSD in children with complex epilepsy implicates some cautiousness. The coinciding symptoms of trauma reactions and symptoms often seen in children with epilepsy may be challenging to differentiate as outlined above, and particularly in children with impaired cognitive functioning. However, it might be beneficial to investigate the possibilities of assessing trauma exposure and reactions in children with more severe epilepsies than possible in this study. More severe epilepsy will generally expose the child to more adverse events. Although, there probably is a lower limit of when it is possible to separate the coinciding symptoms and when it is reasonable to try. The goal of assessing trauma is to target treatment, and it would take

a certain level of function to participate in treatment and benefit from it. However, it would be of interest to explore to what extent this is possible.

5.2. Limitations

Apart from the general methodological considerations and limitations thereof, a considerable limitation of the study is a somewhat low response rate of 49 %. Non-responders indicated that the survey was too demanding to complete while hospitalized with their child, and some found the emotional burden of dealing with the questionnaires too difficult. This could indicate that some of the more burdened parents did not enter the study and that our results might underestimate the impact of complex childhood epilepsy.

Furthermore, it is essential to emphasize that we found symptoms equivalent to parental psychopathology, which is different from establishing a diagnosis of psychopathology. However, the mental distress reflected in the results is yet highly concerning.

Although already discussed in PhD paper II, it is important to highlight that the limited sample size of children assessed for symptoms of PTSD compromises the power of the study. Moreover, assessing three different age groups with different measures of PTSD across the groups further compromises this. However, the strengths of the assessments are that they all are developmentally sensitive, and for children above six years, they reflect the child's experiences.

Furthermore, due to the self-report measure of trauma symptoms in schoolchildren and adolescents, only children with the capabilities to understand and answer the questionnaires were included in the study of PTSD symptomatology. This group of children is solely representative of the better functioning children within more complex and severe epilepsies. As mentioned above, research on trauma exposure and reactions to exposure in children with more severe epilepsy and lower levels

of cognitive functioning might be beneficial. However, it would demand a cautious approach due to the complexity of the condition.

Measures of psychopathology and symptoms of PTSD in children have been described as symptomatology and not a diagnosis of PTSD, just as for the parents.

6. Implications for research and practice

The study results of this thesis supplement the body of international literature concerning the family impact of childhood-onset complex epilepsy. The results further expand on the existing knowledge by demonstrating associations of parental psychological factors of importance to the experience of family impact and parental stress. Such associations have only sparsely been investigated, and further research concerning these associations would help target the support needs of the families in other settings and cultures alike.

To the author's knowledge, our study of child trauma reactions and PTSD with developmental-sensitive standardized assessment tools is the first of its kind. The trauma perspective holds tremendous potential in the sense that treatment possibilities exist, and exposure to trauma as defined by the DMS-5 is to some degree preventable in childhood epilepsy.

Increasing awareness in the scientific literature of trauma exposure and responses in children with epilepsy would be beneficial, and future studies should include larger and more homogenous groups of children. In addition, it would be relevant to assess better functioning children with epilepsy than those included in our study, and it would further be of interest to explore how children with more severe epilepsy can be assessed in a meaningful way.

Finally, it would be valuable to obtain knowledge about the specific consequences of exposure to trauma and adversities. However, it will be challenging to understand the cause-consequence relationship due to the complexity of the condition and differential diagnostics.

However, the results obtained in this study combined with the neurobiological knowledge presented above call for an increased awareness of trauma exposure in clinical settings and other relevant contextual settings without further research.

An important implication of the results in a national context is the obtained understanding of the families we meet at the Danish Epilepsy Center and the possibility of targeting intervention based on the results.

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Appendix A: PhD paper I

Title: The impact of severe pediatric epilepsy on experienced stress and psychopathology in parents

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Keywords; Pediatric epilepsy**,** PTSD, parental stress, psychopathology, caregiver resources.

Highlights

- One in two parents caring for a child with severe epilepsy might be at risk of developing concerning symptoms of mental distress and psychopathology
- Seizure-related traumatic episodes are highly influential for parental distress
- Caregiver resources and the level of the child's behavioral difficulties are reliable indicators for the development of psychopathology in parents

Abstract

Objectives: To assess the prevalence of psychopathology and the level of stress in parents of children with severe epilepsy to gain a better understanding of parental support needs.

Methods: Questionnaires were completed by parents of children with severe epilepsy during the hospitalization of their child at the Danish Epilepsy Center. The questions targeted symptoms of post-traumatic stress disorder (PTSD), complex PTSD (CPTSD), depression and anxiety, and the level of perceived stress.

Results: A total of 162 caregivers of 140 children with epilepsy participated in the survey. Mothers were more often unemployed than fathers (38% vs. 11%, $p<0.01$), and nearly half of the children (47 %) attended special needs classes. Psychopathology symptoms were found in 43.5 % of parents, fulfilling criteria for one or more diagnoses, and an additional 11 % showed symptoms of sub-clinical PTSD. Parent-rated child difficulties were significantly associated with PTSD ($M_{diff} = 5.51$, $p = 0.001$), depression ($M_{diff} = 4.50$, $p < 0.000$), and anxiety ($M_{diff} = 4.61$, $p = 0.01$), and with higher levels of perceived stress ($p < 0.001$).

Conclusion: Caring for a child with severe epilepsy has a significant psychopathological impact on caregivers. Caregivers' resources and the degree of behavioral difficulties in the child, rather than epilepsy-related factors, are highly correlated with distress and psychopathological symptoms in caregivers.

1. Introduction

Severe childhood epilepsy is characterized by treatment-resistant seizures and, typically, concurrent developmental delay. Comorbidities such as intellectual disability, motor limitations, and behavioral problems occur frequently [1-6], requiring the caregivers of a child with severe epilepsy to deal not just with the seizures and their treatment but also challenges in handling everyday life [7, 8]. The mechanisms underlying these comorbidities are complex to assess as the brain undergoes rapid changes during childhood and the child's development takes place in interaction with its surroundings. When assessing causal factors of functional level and developmental delay in a child, it is thus important to pay attention to the nature of the epilepsy and the seizures, the underlying brain damage or dysfunction, the treatment of the seizures [9], as well as ecological factors [10].

Caring for a child with a chronic and life-threatening disease such as severe childhood epilepsy is a predictor of high levels of depression, anxiety, and post-traumatic stress disorder (PTSD) in caregivers [11-16]. Caregiver-perceived stress may challenge the sustainment of a positive caregiver-child relation [17, 18], and more significant behavioral dysfunctions are seen in children where the caregiver-child relation is challenged [19]; this, in turn, imposes more stress on the family [20, 21]. The WHO International Classification of Diseases (ICD-11) recently introduced a distinct diagnosis of more complex symptom representation associated with prolonged exposure to traumatic stressors, 'complex PTSD' (CPTSD), aside from a revised symptom description of PTSD [22, 23]. This new diagnosis might promote better understanding of parents with symptoms of CPTSD that previous psychopathological assessments have not been able to address. Acquiring knowledge about the mental state of caregivers to children with severe epilepsy is a first step to understanding how the needs of caregivers can be met in order to help them regain and preserve their resources.

It is well documented that family factors and the relationship between parent and child have an impact on the development and maintenance of child psychopathology [2, 24, 25]. A recent study

found that the family's level of functioning, perceived stress, and resources to handle stressful situations have a significant influence on the child's emotional well-being two years after seizure onset [26]. Resources within the family are a moderating factor between the severity of epilepsy and the child's emotional well-being [26].

The aim of this single-center, cross-sectional study was to address psychopathology and stress in caregivers of children with severe epilepsy by assessing the prevalence of PTSD and CPTSD and the level of depression and anxiety symptomatology, and by exploring perceived stress in relation to caregiver resources and the degree of the child's difficulties.

2. Methods

2.1. Participants

Parents of children aged 0-18 years were approached for participation in the study when hospitalized with their child at the pediatric department of the only tertiary epilepsy center in Denmark, the Danish Epilepsy Centre, Filadelfia. Participants signed informed consent, and data handling guidelines from the Danish Data Protection Agency were followed. During the 12-month period of data collection, 437 children were hospitalized at least once. Caregivers who were not native Danish speakers and non-biological parents were excluded. In total, parents of 287 children were asked to complete the study survey.

2.2 Measures

Two unidimensional subscales of the Hopkins Symptom Checklist-90 (SCL-90) [27] were used to measure the level of depression (HAM-D_6) and anxiety (SCL-ASS_8) symptomatology [28]. Post-traumatic stress disorder (PTSD) and complex PTSD (CPTSD) symptomatology were assessed using a research version of the International Trauma Questionnaire (ITQ) [29, 30] that was based on the ICD-11 criteria for PTSD and CPTSD diagnoses. CPTSD comprises three symptom clusters additional to the three symptom clusters of the ICD-11 PTSD diagnosis (avoidance, re-experiencing,

and persistent sense of threat). The additional symptom clusters are related to disturbances of self-organization, affective dysregulation, negative self-concepts, and disturbances in relationships [22]. The caregiver's level of perceived stress was measured with the Perceived Stress Scale (PSS-10) [31]. The Multi-dimensional Scale of Perceived Social Support (ZIMET) [32] and the Visual Analogue Scale of Self-control (VAS) [33-35] were used to evaluate external and internal resources in caregivers, respectively. The Strength and Difficulties Questionnaire (SDQ) [36] measured the child's level of difficulties regarding emotional problems, hyperactivity/attention, behavior, and peer difficulties.

Demographic information included gender and age (caregiver and child) as well as caregiver education, job situation, and marital status. The caregiver provided diagnostic information concerning the child, which was later adjusted for eventual misconceptions by a clinician. Epilepsy-related factors included the type of epilepsy, type and frequency of seizures, the child's age at seizure onset, duration of epilepsy, and anti-epileptic drugs (AED). Psychiatric disorders, age at school entry, and current school or day-care facility represented qualitative markers of the child's level of everyday function.

2.3. Statistical analysis

Quantitative statistics were analyzed using IBM SPSS version 24. All questionnaire variables were screened for missing data, and Little's MCAR test was performed. Missing values up to 20 % at item or case level were imputed using the expectation-maximization (EM) method. This method was run for each subdomain in composite scale measures (SCL-90, ITQ, ZIMET, SDQ). Summary statistics were calculated for child factors, sociodemographic factors, caregiver level of PTSD, CPTSD, depression, and anxiety symptomatology. χ^2 analyses were performed to examine the differences in categorical child factors (epilepsy type, seizure type, and frequency) and categorical sociodemographic factors (caregiver gender, marital status, education, and employment status)

between caregivers with and without PTSD, CPTSD, depression, and anxiety symptomatology. Post hoc analysis involved pairwise comparisons using the z-test of two proportions with a Bonferroni correction. Independent-samples T-tests were used to determine the association between child factors and symptomatology. The level of statistical significance was set at $p < 0.05$.

Multiple linear regression analyses were performed to assess caregiver-perceived stress (PSS-10); possible predictive caregiver- and child-associated variables were first tested for their bivariate correlation with the caregiver's level of perceived stress and were entered into the regression if they were correlated at $p < 0.20$. Assumptions of residual normality, linearity, and homoscedasticity were assessed. Multicollinearity among the explanatory variables was assessed using the variance inflation factor (VIF).

3. Results

The survey was completed by 162 caregivers (of whom 125 were women) aged 27-60 years (mean 39.8 years, SD 6.7) of 140 children with epilepsy, giving a response rate of 49 %. The children had a mean age of 8.9 years (0-18 years; SD 4.6) and mean duration of epilepsy of 4.03 years (SD 3.72). Nearly half of the children (47 %) attended special needs classes, and 38 % had a deferred school entry, indicating some degree of delayed development (Table 1).

Seventy-two percent of the parents lived together with the other biological parent, and 65 % had a part-time or full-time job. Mothers were more often unemployed than fathers (38% vs. 11%, $p<0.01$), and two-thirds of the unemployed mothers (24 %) were compensated full-time for loss of earnings due to illness severity, compared to 3 % of fathers.

Table 1: Group Characteristics

Child	
Number of patients (girls %)	140 (46)
Age, *M* (SD)	8.9 (4.56)
Years with epilepsy, *M* (SD)	4.0 (3.72)
Epileptic diagnosis, *n* (%)	
Epileptic encephalopathy	26 (19)
Focal/multifocal epilepsy	73 (52)
Idiopathic generalized epilepsy	20 (15)
ESES/CSWS	21 (14)
Seizure frequency, *n* (%)	
Seizure-free	37 (30)
Daily seizures	42 (34)
Weekly or less often seizures	44 (36)
Attended school later than expected, *n* (%)	40 (38)*
School for children with special needs, *n* (%)	49 (47)*
Psychiatric diagnosis, *n* (%)	16 (15)*
Caregiver	
Number of parents (women %)	162 (77)
Civil status, *n* (%)	
Both parents living together	117 (72)
Work situation, *n* (%)	
Employed	106 (65)
Compensated for loss of earnings	29 (18)

* *n*=105, age > 5.

3.1. PTSD, C-PTSD, depression, and anxiety

The response rate for the ITQ questionnaire was 81 % (n=132). Of this group, 26 (20 %) gave answers equivalent to the symptomatology of a PTSD diagnosis, and an additional 25 (19.2 %) had sub-clinical symptoms as they reached cut-off scores on two out of three symptom clusters. One-third of those with PTSD symptomatology also exhibited symptoms equivalent to CPTSD (6.9 %). Of the 26 caregivers with a PTSD symptomatology, 73 % showed co-occurring symptoms of moderate (26 %) to severe (47 %) depression.

The prevalence of depressive symptomatology among the 152 respondents was 34.9 %, of whom 15.8 % had symptoms of severe depression and 19 % of moderate depression. Symptoms of anxiety (152 respondents) were found in 14.5 % of parents overall and in half of the parents with a co-existing PTSD (53 %). Hence, in total, 43.5 % of the parents showed symptoms of psychopathology by fulfilling the criteria for one or more diagnoses, and an additional 11 % showed symptoms of sub-clinical PTSD alone.

There were no statistically significant differences in the caregiver's gender concerning PTSD, CPTSD, depression, or anxiety symptomatology. However, the prevalence of PTSD symptomatology was significantly higher in caregivers living alone or divorced than in biological caregivers living together (Table 2a). There were no differences in the level of depression or anxiety related to marital status. Caregivers without current employment displayed a higher level of PTSD (χ^2 (1) = 5.323, p = 0.021), depression symptoms (χ^2 (1) = 9.853, p = 0.002), and anxiety symptoms (χ^2 (1) = 12.118, p < 0.000) than caregivers having a part-time or full-time job. Parents with more than five years of education after primary school showed a significantly lower prevalence of PTSD (χ^2 (1) = 6.639, p = 0.010) and anxiety symptoms (χ^2 (1) = 7.134, p = 0.008) than parents with fewer years of education (Table 2a).

Table 2a: Sociodemographic Features of Parents with or without PTSD/CPTSD (n = 132)

	Total sample	PTSD	No PTSD	*p*
Mother, *n* (%)	101 (78)	22 (85)	79 (76)	0.343
Divorced or living alone *n* (%)	34[b] (26)	11 (42)	23 (22)	0.039
Unemployed *n* (%)	44[c] (34)	14 (54)	30 (30)	0.021
< 5 yrs education	81[b] (61)	22 (85)	59 (57)	0.010

[a]*Fischer's Exact Test,* [b]*n=129,* [c]*n=127*

Parent-rated child difficulties (SDQ) were significantly associated with symptoms of psychopathology compared to parents without symptoms. The mean difference (M_{diff}) for PTSD was 5.51, 95% CI [2.35, 8.75], $t(115) = -3.438$, $p = 0.001$, $d = 0.80$; for depression $M_{diff} = 4.50$, 95% CI [2.08, 6.92], $t(136) = -3.672$, $p < 0.000$, $d = 9.68$; and for anxiety $M_{diff} = 4.61$, 95% CI [1.12, 8.10], $t(136) = -4.606$, $p = 0.010$, $d = 0.67$, where more difficulties were associated with higher prevalence of psychopathology.

No other child-related factors or epilepsy-specific factors were individually significantly associated with PTSD, depression, or anxiety. However, there was a relatively higher representation of caregivers (40 %) with symptoms of PTSD to children with CSWS (continuous spike and wave during slow-wave sleep) than other types of epilepsy. Nearly one-third of caregivers of children with daily seizures showed symptoms of PTSD compared to 14 % of caregivers of seizure-free children and 18 % of caregivers to children with weekly or less frequent seizures. Of the parents who had experienced their child having status epilepticus, 66 % showed symptoms of depression, anxiety, PTSD, or sub-clinical symptoms of PTSD. Symptoms of anxiety were present in 30 % of parents to a child with a psychiatric diagnosis (Table 2b).

Table 2b: Child Variables for Parents with or without PTSD/CPTSD (n = 132)

	Total sample	PTSD	No PTSD	*p*
Child psychiatric diagnosis, *n* (%)[a]	13 (10)	3 (12)	10 (10)	0.719
Free from seizures, *n* (%)	28 (22)	4 (15)	24 (23)	0.307
ESES/CSWS, *n* (%)	20 (15)	8 (31)	12 (12)	0.066
Status epilepticus, *n* (%)	37[d] (30)	11 (44)	26 (26)	0.078

[a]*Fischer's Exact Test,* [d]*n=125*

Among the fifteen pairs of caregivers where both parents completed the survey, PTSD symptomatology was present in five couples. In one couple, both caregivers displayed symptoms equivalent to a PTSD diagnosis. A sub-clinical level of PTSD symptomatology was present in two other couples where one caregiver had symptoms of PTSD.

3.2. Perceived stress

The mean score of the PSS-10 scale was 20.18 (SD 8.51), with a higher score for parents without current employment (Table 3). There were no differences in score levels related to caregiver gender, or whether parents were living together or not. A higher level of perceived stress was associated with younger age of the child and a higher level of the child's difficulties. Seizure type, seizure frequency, epilepsy category, and age at seizure onset were *not* significantly associated with the level of the caregiver's stress.

Table 3: Means, Standard Deviations, and Intercorrelations for Caregiver-Perceived Stress, Caregiver Resources, and Epilepsy-Related Factors

	M	*SD*	1	2	3	4	5
Perceived stress	20.18	8.51	-0.19**	0.46***	-0.21**	0.61***	0.43***
1. Age, child	8.81	4.58	-	-0.17*	0.32***	-0.19**	-0.01
2. Child difficulties	16.02	6.98		-	-0.05	0.26**	0.25**
3. Job situation	0.68	0.47			-	-0.36***	-0.12
4. Control of own situation	4.37	3.11				-	0.35***
5. Social support (inv. sq. root)	4.07	1.65					-

$^{*}p<0.05$. $^{**}p<0.01$. $^{***}p<0.001$.

The caregiver's social support and the experience of having control over life circumstances were associated with a lower level of perceived stress. However, when entering all relevant variables into a standard multiple regression analysis, only social support, the child's difficulties, and control of own

situation were significant predictors of the level of the caregiver's stress when controlling for the remaining variables (Table 4).

Table 4: Linear Regression Analysis Summary for Caregiver and Child Variables Predicting Caregiver-Perceived Stress

	B	95% CI	β	*t*	*p*	sr^2 (unique)
Age, child	-0.13	[-0.37, 0.12]	-0.07	-1.01	0.317	0.00
Child difficulties	0.33	[0.17, 0.50]	0.27	4.12	0.000	0.07
Job situation	0.24	[-2.26, 2.74]	0.01	0.20	0.849	0.00
Control of own situation	1.24	[0.85, 1.63]	0.46	6.31	0.000	0.15
Social support (inv. sq. root)	1.06	[0.37, 1.75]	0.20	3.02	0.003	0.03

Adj. R^2=0.48, R=0.70, p<0.000.

4. Discussion

The study results indicate that caring for a child with severe childhood epilepsy has a significant psychopathological impact on caregivers. While 89 % of the fathers were in employment, only 62 % of mothers were employed. This compares to the general Danish workforce aged 35-44 years at the time of survey completion, where 93 % of men and 85 % of women were employed [37]. Most of the unemployed mothers were compensated full-time for the loss of earnings due to illness. The severity of illness was reflected in the children's high level of individual requirements. Nearly half of them were attending special needs classes, and one-third had a deferred school entry. These prevalences are ten and five times higher, respectively, than for the general population of school-seeking children in Denmark [38]. This emphasizes that caregivers of children with severe epilepsy are dealing with more than just seizures and their treatment.

Caregivers with less than five years of education after primary school and without current employment showed higher prevalence of psychopathological symptoms and a higher level of

perceived stress than parents with higher educational levels and parents having a part-time or full-time job. These findings are supported by studies on families of children with severe or chronic illnesses, however not consistently [39, 40].

The study results further indicate that it is more often the mothers than the fathers who take on the responsibility of the daily care of the severely ill child and are the more exposed family caregiver when it comes to maintaining external and internal resources.

The prevalence of parental psychopathology in our sample resembles the spectrum of prevalence found in other studies on caregiver psychopathology concerning PTSD [11, 13, 41], depressive disorders [42], and anxiety [12]. The co-occurring prevalences of depression (73 %) and anxiety (53 %) within caregivers with PTSD symptomatology were also at the level of previous findings [13, 43]. However, in contrast to most studies [11, 44], we did not find gender differences related to the prevalence of psychopathology. We found a prevalence of 6.9 % with CPTSD, which is slightly higher than in non-clinical populations [45, 46].

To our knowledge, this study is the first that explores parental CPTSD in families with chronic or severe childhood illness, so comparisons to studies with childhood epilepsy or other childhood illness are not possible. Despite their relatively few numbers, however, it is important to be aware of this group of caregivers. They might require more support and intervention than caregivers with PTSD or other psychopathology.

Although not statistically significant, we found a higher prevalence of PTSD in caregivers of children with CSWS than other types of epilepsy, and in parents of children with daily seizures compared to less frequent seizures. CSWS is an epileptic encephalopathy that presents with neurocognitive regression and clinical seizures and demonstrates an electroencephalogram (EEG) pattern of electrical status epilepticus during sleep. CSWS is an age-related condition, typically presenting in children around five years of age, with evolving learning disabilities and loss of

cognitive abilities [47]. The ongoing awareness of the cognitive changes and difficulties due to abnormal brain activity lasting from months to years could be a source of persistent psychological stress to parents. Furthermore, experiencing a child having status epilepticus was associated with high levels of psychopathology and sub-clinical levels of PTSD symptomatology (66 %). Experiencing a child having a status episode leaves parents powerless and in fear of losing their child instantly. A concern of whether the episode might have caused harm to the child's brain and cognitive abilities often follows [48-52]. This concern could be similar to that of children with daily seizures.

We found significant positive associations between parent-rated child difficulties (SDQ) and prevalence of psychopathology, and a correlation with higher perceived stress levels, in accordance to research concerning parents of childhood illnesses in general [53] as well as parents of children with epilepsy [7]. Most (72 %) of the parents lived together, which is higher than the general population in Denmark [54]. Studies on divorce rates in families with severe or chronic childhood illnesses show similar divorce rates as general families despite the presence of a high level of marital distress [55, 56]. Biological parents living together had a lower prevalence of PTSD than divorced parents or parents living alone, indicating a protective factor of co-parenting. However, we found a high prevalence of PTSD or a sub-clinical level of PTSD in partners of caregivers with PTSD symptomatology (three out of five couples), which should be taken into consideration when assessing family resources. Finally, our study showed that a higher level of perceived stress was associated with younger age of the child, indicating a need for special attention to this group of caregivers. Associations between increased levels of parental mental health difficulties and child behavior difficulties were found in a study concerning parents of younger children with epilepsy [57]. The association's direction was not established in the study, however, as noted in the discussion of the study, younger children might have an increased risk for behavioral difficulties [57]. This suggested association corresponds to our findings related to significant correlations between child behavior

difficulties and parental symptoms of psychopathology and distress. Moreover, if caregivers had sufficient social support and control over life circumstances, they experienced less stress. This suggests that an awareness of their social network and the opportunities for assistance in keeping in control of their own life could help parents to maintain their coping resources. These findings correspond to known factors of resilience in parents of children with developmental disabilities [58].

This study is the first of a series of studies assessing the impact of severe childhood epilepsy on family resources in a Danish population. The overall goal is to better understand the needs for individualized support in different family situations.

5. Limitations

A relatively high number of caregivers declined to participate in the survey when approached. Feedback from non-responders indicated this was partly due to the emotional burden of dealing with the questionnaires, and some found it too demanding to complete the survey while hospitalized with their child. This could indicate that some of the more burdened parents did not enter the study and that our results might underestimate the impact of severe childhood epilepsy.

We used self-completed questionnaires to assess symptoms of psychopathology and to collect epilepsy-related data. These self-report data are likely to be more sensitive to subjective understandings or misinterpretation of questions than a diagnostic interview conducted by a trained clinician. However, a pediatric neurologist corrected the diagnostic information as far as possible in the case of parental misconceptions. We further emphasize that we found symptoms equivalent to psychopathology, which is different from establishing a diagnosis of psychopathology.

6. Conclusion

The impact on parents who care for a child with severe epilepsy is profound. The caregiver's resources and the degree of behavioral difficulties in the child, rather than epilepsy-related factors,

are highly correlated with distress and psychopathological symptoms in caregivers. Coping interventions for families with childhood epilepsy should include support aimed at maintaining parental resources and take into consideration the parents' capacities to handle the child's behavioral difficulties.

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Conflicts of Interest

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

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Appendix B: PhD paper II

Title: Post-traumatic stress disorder (PTSD) symptoms in children with severe epilepsy

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Keywords; Pediatric epilepsy**,** PTSD, psychopathology, behavioral difficulties

Highlights

- Knowledge of trauma symptoms and associations in children with epilepsy is sparse.
- The first study to assess PTSD with developmental-sensitive assessment tools.
- Results indicate concerning prevalence of clinical and subclinical PTSD symptoms.

Abstract

Objectives: To assess symptoms of post-traumatic stress disorder (PTSD) in children with severe epilepsy and the associations of trauma symptoms across age, comorbid symptoms, epilepsy-specific factors, parental resources, and psychopathology.

Methods: 50 children with severe epilepsy across three different age groups (0-5 yrs., 6-12 yrs., 13-18 yrs.) were assessed with developmental-sensitive and standardized PTSD assessment tools when hospitalized at the tertiary epilepsy center Filadelfia, Denmark. The Diagnostic Infant and Preschool Assessment (DIPA), the Darryl test, and the ITQ questionnaire were used to assess the three age groups, respectively.

Results: Twenty-two percent of the overall sample met the criteria for PTSD, with a prevalence of symptoms increasing with age (6%, 28%, and 40%). Comorbid psychiatric symptoms in preschoolers were present in 81% of the children witnessing a high level of distress in this group. Behavioral difficulties were elevated across all three age groups, and 40% of the children with trauma symptoms had a parent with concurrent psychopathology.

Conclusion: To the authors' knowledge, this study is the first to assess trauma symptoms with standardized tests in children with more complicated epilepsies. Trauma symptoms in the group are high; however, there is a need for larger scale studies and research into trauma symptoms in children with more severe epilepsy than those assessable with the included assessment tools. The trauma perspective in severe childhood epilepsy might further clarify the complex associations of biological and contextual variables that affect the children's life quality and enable better preventative treatment options for this group.

1. Introduction

Childhood-onset epilepsy is associated with psychiatric and medical comorbidity [1–7] and cognitive, behavioral, and psychosocial difficulties [8-11]. Scandinavian nationwide cohort studies have demonstrated that up to 80% of children with epilepsy have one or more comorbid disorders [12] and have elevated risks of developing psychiatric disorders in later life [13]. The quality of life in children with epilepsy has been shown to differ from that of healthy peers [14]. However, the comorbidity of childhood epilepsy seems to be a superior predictor of impacted life quality [15,16] compared to illness-specific factors.

Increasing awareness of the factors beyond biological causes of comorbidity and life quality in children has emerged over the past two decades. Studies have demonstrated the influence of family factors [17,18] and the social context [19,20] on the development of child psychopathology and point to a contextual understanding of impacted life quality in children with epilepsy [21]. Family resources [22,23] and socioeconomic status [24,25] influence how the child's experience affects life quality alongside comorbidity factors. We further know that family resources are highly compromised by concerning levels of parental stress and psychopathology in caregivers of children with epilepsy [26–31].

Trauma studies have demonstrated that adversities in early childhood have a significant influence on a child's developmental trajectory [32] and subsequent adult onset of psychiatric diagnoses [33], as well as diminished physical health [34,35]. It is further apparent that a child's development is influenced by the care pro vided by their parents in times of distress and that this care might be compromised by parental stress and psychopathology [35–37].

In the recently updated DSM-5 post-traumatic stress disorder (PTSD) diagnosis [38], the criteria for traumatization include if a person is directly exposed to a traumatic event, is witnessing it, learning that a relative was exposed to it, or indirectly by exposure to distressing details of an event,

such as repeatedly hearing details about it. The diagnostic criteria for PTSD in children and adolescents are comparable to that of adults. However, children experience and express the symptoms differently depending on age and developmental stage [39]. See Elklit et al. [40] for a thorough comparison across preschool children (age 0–6 years), school children (age 7–11 years), and adolescents (age 12–18 years).

Furthermore, the theory about and research into secondary traumatization [41] states that the consequences of trauma exposure are not limited to the person who has been exposed to it but can also affect close relatives, such as a child. The parent can transfer their psychological symptoms to their child directly, in the sense that the child develops the same symptoms, or indirectly, by the child getting affected by his/her parent's moods, fears, behaviors, or narratives, which influences the child's function and development [42].

The incidence of traumatic experiences in childhood epilepsy is high and is likely experienced differently by the child depending on age and diagnosis. With a further mind on secondary traumatization, it seems important to examine if PTSD could be a possible outcome in children with severe epilepsy.

Hence, the primary aims of this study were to investigate trauma symptoms in children with severe epilepsy and compare the symptoms across different ages, other comorbidity measures, and epilepsy-specific factors. Secondly, we examine the associations between trauma symptoms and caregiver resources and symptoms of psychopathology. This study is the first to investigate the prevalence of PTSD in children with severe epilepsy to the authors' knowledge.

2. Methods

2.1. Participants

Parents and their children (aged 0–18 years) were recruited during the child's hospitalization at the pediatric department at the Danish Epilepsy Centre, Filadelfia. The Epilepsy Centre is a tertiary

healthcare provider, and children submitted to hospitalization have a severity of epilepsy that demands specialist care. Informed consent was collected from parents for their own and their child's participation in the study. Adolescents at the age of 15–18 years were informed about the study regarding PTSD symptomatology and were entitled to decline participation. Data handling guidelines from the Danish Data Protection Agency were followed. We excluded non-biological parents and caregivers as well as children who were not native Danish speakers. Parents of 140 children were enrolled in the survey; however, not all children could participate in the survey of PTSD symptomatology due to the severity of their epilepsy or cognitive disability. Children above the age of 6 years who were attending school activities at the hospital during their hospitalization or otherwise were evaluated to be able to read and write or understand verbal given messages sufficiently to answer the questionnaires were eligible to participate in the survey of child and adolescent PTSD. Parents of children below the age of seven were asked to complete an interview about their child if the parent stated that the child could communicate with the parent. In total, 50 children and caregivers were included in the study about child PTSD symptomatology. The remaining 90 parent–child dyads were included as a comparison group of child and parent characteristics.

2.2. Procedure

The caregivers provided information about sociodemographic factors, parental stress and psychopathology, child diagnostic factors, and child executive functioning and behavioral difficulties during their stay at the hospital. A trained clinician interviewed 16 parents of children aged 0–5 years to assess child psychopathology symptoms. The interview followed the semi-structured interview guide; Diagnostic Infant and Preschool Assessment (DIPA) [43]. Twenty-nine children aged 6–12 were asked to complete the cartoon-based Darryl test [44] when participating in school activities together with a teacher during hospitalization or with the guidance of a psychologist. Five adolescents aged 13–18 years were handed the ITQ questionnaire [45] to complete independently. A trained

clinician was at the disposal if the adolescent needed help to fill out the questionnaire. The Darryl test and ITQ questionnaire assess symptoms of PTSD solely.

Table 1: Group characteristics

	Included	Not included
Child characteristics		
Number of patients (girls %)	50 (54)	90 (41)
Age, M (SD)	10.3 (2.8)	8.9 (5.0)
Years with epilepsy, M (SD)	4.2 (3.4)	4.1 (4.0)
Epileptic diagnosis, n (%)		
Epileptic encephalopathy	5 (10)	21 (23)
Focal/multifocal epilepsy	26 (52)	47 (52)
Idiopathic generalized epilepsy	10 (20)	10 (11)
ESES	9 (18)	12 (13)
Seizure frequency, n (%)		
Seizure-free	16 (32)	21 (23)
Daily seizures	16 (32)	26 (29)
Weekly or less often seizures	12 (24)	32 (36)
Attended school later than expected, n (%)	13* (33)	29** (45)
School for children with special needs, n (%)	13* (33)	36** (55)
Psychiatric diagnosis, n (%)	3* (8)	13** (20)
Executive function, M (SD)	85.2 (12.2)	79.5 (17.1)
Behavioral difficulties total score, M (SD)	15.3 (6.1)	16.4 (7.7)
Caregiver characteristics		
Number of parents (women), n (%)	50 (76)	90 (82)
Both parents living together, n (%)	34 (68)	63 (72)
Employed, n (%)	36 (75)	54 (60)
Perceived Stress, M (SD)	20.1 (7.7)	20.8 (8.6)
PTSD, n (%)	11 (28)	36 (40)
Depression, moderate, n (%)	10 (25)	14 (16)
Depression, severe, n (%)	3 (8)	17 (19)
Anxiety, n (%)	6 (15)	13 (14)

* n=40/ **n=65, age > 5.
M = mean. SD = standard deviation. ESES = Electrical status epilepticus during slow-wave sleep. PTSD = post-traumatic stress disorder.

2.3. Measures

2.3.1. Child psychopathology

The DIPA is a clinical semi-structured interview administered to the caregiver of children under the age of seven [43]. The interview consists of 517 questions used to identify symptoms across 13

different psychiatric disorders. The interview is validated across different countries and has proved to be a sensitive tool when measuring psychiatric disorders in preschool children [46-48]. The PTSD section of the interview lists 11 possible traumatic events, which the parent answer on behalf of the child and, if more than one, rate the worst. Next, 55 questions related to re-experiencing, avoidance, and arousal behavior/reactions related to the worst event follow, and lastly, a section of the degree of functional impairment is assessed. The criterion of a PTSD diagnosis is met if the child has one symptom of re-experiencing, three avoidance symptoms, two arousal symptoms, and one functional impairment symptom. A validated Danish version of DIPA was used in this study [47]. Diagnostic symptoms are based on the DSM-IV [49].

Darryl's cartoon test is a screening tool used to identify and measure PTSD symptoms in children and adolescents [44,50]. The test consists of 23 cartoons of a pre-adolescent boy named Darryl, accompanied by three empty, half-full, and full thermometers. A text about the psychological response specific to an illness related experience is read to the child. The experience is illustrated in the feelings of Darryl depicted in the cartoon. The child then has to identify if he or she feels the same way as Darryl and circle the thermometer that best matches the child's feelings. Nineteen cartoons are related to trauma symptoms, re-experiencing; 7, avoidance; 7, and arousal; 5. The symptom criteria are met if the child appoints a half-full or full thermometer. The cluster criteria are met for one symptom of re-experiencing, three symptoms of avoidance, and two arousal symptoms. If all three cluster criteria are met, the criterion of PTSD is fulfilled. A subthreshold of PTSD (sub-clinical level) requires two out of three cluster criteria.

The test assesses PTSD symptoms in a developmentally appropriate manner [50] and is validated for a Danish population with good internal consistency for the overall scale ($\alpha = 0.88$) [51]. Since the test has yet to be systematically validated for the DSM-5, the DSM-IV is referenced in the current study.

The International Trauma Questionnaire (ITQ) [52,53] is a 12 item self-report measure for the assessment of the ICD-11 [54] criteria for PTSD and complex PTSD (CPTSD) [55]. Six items are included in the clusters of re-experiencing, avoidance, and sense of threat (two items in each cluster). For a probable diagnosis of PTSD, one symptom is required in each of the clusters for re-experiencing, avoidance, and sense of threat, as well as a score of two or more on one of the three questions assessing associated functional impairment. A subthreshold of PTSD (sub-clinical level) requires two out of three cluster symptoms present. Items assessing functional impairment were unavailable for the current sample; hence, results are referred to as symptoms of PTSD. In this current study, measures of CPTSD were not included for the adolescents. The scale has been under several revisions since the initial version of the ITQ [45], and items consistent with the final version of the ITQ were used for the current analyses. A version for children and adolescents has been proposed (ITQ-CA) [56]; however, the version has yet to be validated in Denmark. The construct validity of the ITQ scale has been validated in child and adolescent populations aged 10–18 years [57,58].

2.3.2. Child characteristics

The Strength and Difficulties Questionnaire for Parents (SDQ-P) [59] measured the child's level of behavioral difficulties and prosocial behavior. The parent completes the questionnaire. The SDQ is a widely used and reviewed 25-item questionnaire [60-62] and is validated for a Danish population [63].

The Comprehensive Executive Function Inventory (CEFI) [64] is a behavior rating scale of executive-function strengths and weaknesses. The rating scale contains 100 items, with 90 items covering ten different executive skills. The total scale was used as a proxy measure for the child's level of cognitive functioning in this study. Parents completed the rating scale for children above the age of 6. The scale has strong psychometric properties and is valued within research and clinical practice [65].

2.3.3. Parental stress

The caregiver's level of perceived stress was measured with the 10-item Perceived Stress Scale (PSS-10) [66]. The scale is a self-reported questionnaire that evaluates the degree to which individuals have experienced their lives as stressful during the previous month. It has shown acceptable psychometric properties across various cultures and countries [67].

2.3.4. Parental psychopathology

Two unidimensional subscales of the Hopkins Symptom Checklist-90 (SCL-90) [68] were used to measure symptoms of depression (HAM-D6) and anxiety (SCL-ASS8). The subscales are validated for a Danish population [69,70].

The International Trauma Questionnaire (ITQ) scale equivalent to that of the one used for the adolescents [52,53,55] was used to assess symptoms of PTSD in parents.

Epilepsy-related factors included the type of epilepsy, frequency of seizures, the child's age at seizure onset, and years with epilepsy. Demographic information included gender and age (caregiver and child), caregiver education, job situation, and marital status.

2.4. Analysis

Results were analyzed using IBM SPSS version 24. A PTSD symptom algorithm, based on DSM-IV, was used to determine how often preschool- and schoolchildren experienced symptoms within the last month. This algorithm requires at least one symptom from the re-experiencing cluster, three (or more) symptoms from the avoidance cluster, and two (or more symptoms) from the arousal cluster. Further symptoms of psychopathology for preschool children were summarized based on DSM-IV. An algorithm based on ICD-11 was used to assess PTSD symptoms within the last month for the adolescents. The algorithm requires at least one of two symptoms from the re-experiencing, avoidance, and threat clusters. Bivariate analyses were performed to assess associations between child symptomatology and caregiver/epilepsy-related variables, respectively.

The Danish National Committee on Health Research Ethics, the Committee Act, section 14(2), was followed for data collection and handling.

3. Results

The study participants were a subsample of a previously described sample from a cross-sectional study, including 140 children with severe epilepsy and 162 caregivers [27, 71]. The fifty included children in the PTSD analyses had a mean age of 10.3 years (0-18 years; SD 2.8) and a mean duration of epilepsy of 4.2 years (SD 3.4) (Table 1). Data on the non-included children (n = 90) are described in Table 1 for comparison.

3.1. Symptoms of PTSD

The overall prevalence of PTSD symptomatology across the three age groups was 22%. The prevalence was increasing with age, with 6% in preschoolers (0–5 yrs.), 28% in schoolchildren (6–12 yrs.), and 40% in adolescents (13–18 yrs.) (Table 2 and 3). Table 2 shows the distribution of re-experience, avoidance, and arousal symptoms for schoolchildren and adolescents. Symptoms are endorsed in schoolchildren if they have answered 'some of the time' or 'a lot of the time' and for adolescents, if they have answered 'moderately', 'very often', or 'extremely often' for each question within the last month. The table also shows the prevalence of subclinical PTSD symptoms, where two of three symptom clusters are present. Collectively, 69% of schoolchildren and 80% of adolescents have PTSD symptoms or subclinical symptoms of PTSD. Characteristics of school-children meeting 0–3 cluster symptoms are presented in Table 5.

Table 2. Descriptive statistics of post-traumatic stress disorder (PTSD) symptoms for schoolchildren and adolescents

	Schoolchildren (6-12 yrs.) *n* = 29	Adolescents (13-18 yrs.) *n* = 5
Re-experience, *n* (%)		
Intrusive thoughts	17 (59)	
Repeated play	4 (14)	
Nightmares trauma related	4 (14)	1 (20)
Nightmares in general	15 (52)	
Flashbacks	7 (24)	1 (20)
Emotional reactions	5 (17)	
Physiological reactions	3 (10)	
Avoidance, *n* (%)		
Internal stimuli avoidance	15 (52)	3 (60)
External stimuli avoidance	4 (14)	2 (20)
Memory lapses	18 (62)	
Dislikes to usual likes	7 (24)	
Emotional limitations	4 (14)	
Feeling of a limited future	4 (14)	
Social withdrawal	8 (28)	
Arousal, *n* (%)		
Trouble sleeping at night	18 (62)	
Irritability	17 (59)	
Concentration	20 (69)	
Hypervigilance	6 (21)	1 (20)
Exaggerated startle	10 (35)	2 (40)
PTSD symptoms	8 (28)	2 (40)
Subclinical PTSD symptoms	12 (41)	2 (40)

The age at which the child was diagnosed with epilepsy was significantly associated ($t(42) = -2.56$, $p = 0.01$) with PTSD symptomatology (Table 4). Children with PTSD symptoms had a later onset of epilepsy (mean age 7.4 years) than children with no symptoms. No other child or parent-related variables were significantly associated with symptoms of PTSD; however, some qualitative differences are worth noticing. Children with PTSD symptoms had a level of executive functioning within the normal range, whereas children with no symptoms had a level below the normal range. On

the contrary, children with PTSD symptoms had more behavioral difficulties than children with no symptoms. Children with focal or multifocal seizures and seizures weekly or less often (not seizure-free) had three to four times higher occurrence of PTSD symptomatology than children with other types of epilepsy or seizure frequency. On further notice, however not statistically significant, 40% of children with PTSD symptomatology lived with a parent with symptoms of psychopathology (Table 4).

Table 3. Descriptive statistics of diagnostic symptoms for preschool children (0-5 yrs.), n = 16

	n (%)
PTSD	1 (6)
Depression	3 (19)
Attention-deficit disorder	6 (38)
Hyperactivity disorder	5 (31)
Oppositional defiant disorder	3 (20)
Conduct disorder	1 (6)
Separation anxiety disorder	3 (19)
Specific phobia	4 (25)
Social phobia	1 (6)
Reactive attachment disorder	1 (6)
Sleep onset disorder	5 (31)
One or more diagnostic symptom total	13 (81)

PTSD = post-traumatic stress disorder.

3.2. Child behavior difficulties

The mean level of child behavior difficulties across all three age groups for the entire sample (*n* = 124) was elevated compared to Danish norms (Table 6). The hyperactivity score and prosocial behavior were problematic across all three age groups, with more significant difficulties regarding hyperactivity and lower prosocial behavior levels than the norms. Except for the preschoolers, the children included in the PTSD analyses had marginal, however not significantly, lower behavioral difficulties than those not included.

Table 4. Child and caregiver variables for children with and without PTSD symptoms

	PTSD	No PTSD
Age at diagnosis, *M* (SD)	7.4 (2.8)*	4.2 (3.6)
Years with epilepsy, *M* (SD)	2.3 (2.5)	4.3 (3.3)
Child age, *M* (SD)	9.7 (4.0)	8.9 (3.5)
Executive function, *M* (SD)	86.8 (14.8)	83.5 (11.6)
Behavioral difficulties, *M* (SD)	18.1 (7.9)	14.7 (5.3)
Epilepsy diagnosis		
Epileptic encephalopathy	0%	
Focal/multifocal epilepsy	35%	
Idiopathic generalized epilepsy	10%	
ESES	11%	
Seizure frequency		
Seizure-free	13%	
Daily seizures	6%	
Weekly or less often seizures	42%	
Caregiver psychopathology	40%	
PTSD	10%	
Depression, moderate	27%	
Depression, severe	9%	
Anxiety	18%	
Perceived stress, *M* (SD)	18.9 (8.3)	20.0 (8.5)

*Bivariate analyses demonstrated a significant difference at the $p < 0.05$ level. M = mean. SD = standard deviation. PTSD = post-traumatic stress disorder. ESES = Electrical status epilepticus during slow-wave sleep.

3.3. Symptoms of psychopathology in preschool children

Except for bipolar disorder, symptoms of all other measured psychiatric disorders by the DIPA interview were present in the preschool sample (n = 16) (Table 3). Of notice are the prevalence of attention-deficit disorder (38%), hyperactive disorder (31%), specific phobia (25%), and sleep onset disorder (31%). In total, 81% of the preschool children had symptoms of one or more psychiatric comorbidity.

4. Discussion

The results indicate that children with severe epilepsy experience elevated trauma symptoms and that trauma symptoms increase with age in this group. Despite lower levels of PTSD symptoms

in preschoolers, comorbid psychiatric symptoms are as high as 81% for one or more psychiatric comorbidity symptoms. A further significant number of children and adolescents come out with symptoms equivalent to subclinical symptoms of PTSD (41% and 40%, respectively).

Table 5. Post-traumatic stress disorder (PTSD) cluster symptoms for schoolchildren (6-12 yrs.), n = 29

	Number of cluster (re-experiencing, avoidance, arousal)			
	0	1	2	3
Girls, *n* (%)	3 (75)	2 (40)	7 (58)	3 (38)
Years with epilepsy, *M* (SD)	4.8 (3.9)	3.2 (2.8)	4.6 (3.0)	1.43 (0.8)
Executive function, *M* (SD)	84.5 (11.6)	91.3 (16.0)	86.2 (6.0)	84.7 (16.0)
Behavioral difficulties, *M* (SD)	13.5 (5.2)	11.2 (8.4)	16.4 (4.0)	19.3 (6.9)
Epileptic encephalopathy, *n* (%)	0 (0)	0 (0)	1 (100)	0 (0)
Focal/multifocal epilepsy, *n* (%)	2 (13)	4 (25)	3 (19)	7 (44)
Idiopathic generalized epilepsy, *n* (%)	2 (33)	1 (17)	3 (50)	0 (0)
ESES, *n* (%)	0 (0)	0 (0)	5 (100)	1 (0)
Seizure-free, *n* (%)	2 (20)	2 (20)	5 (50)	1 (10)
Daily seizures, *n* (%)	1 (17)	1 (17)	3 (43)	1 (17)
Weekly or less often seizures, *n* (%)	1 (11)	2 (22)	2 (22)	4 (44)
Parental psychopathology, *n* (%)	1 (8)	1 (8)	7 (54)	4 (31)
Perceived parental stress, *M* (SD)	17.3 (2.2)	13.2 (7.4)	24.7 (5.4)	19.4 (7.6)

M = mean. SD = standard deviation. n = number.

These children are important to recognize since they do not differ significantly in terms of impairment or distress from children who meet full criteria for PTSD [72]. In comparison to a population study including children who had experienced low-magnitude stressors (events not qualifying as a traumatic event), the prevalence of subclinical PTSD was found in <1% [73]. In this perspective, our findings are concerning irrespective of the magnitude of stressors the included children in our study have been exposed to. Additionally, behavioral difficulties are elevated across all ages, with hyperactivity difficulties and prosocial behavior as the areas of concern in all three age groups.

Table 6. Means and standard deviations (SD) for strengths and difficulties scores compared to validated Danish norms

	Preschool children (2-5 yrs.)		Schoolchildren (6-10 yrs.)		Adolescents (11-18 yrs.)	
	Included *n* = 9	Not included *n* = 17	Included *n* = 23	Not included *n* = 25	Included *n* = 17	Not included *n* = 33
Emotional problem score	3.4 (1.9)	3.2 (3.1)	4.1 (2.8)	4.2 (2.4)	4.3 (2.7)	3.9 (2.5)
Conduct problems	2.8 (2.2)	2.9 (2.3)	3.0 (2.0)*	3.0 (1.7)*	1.7 (1.6)	2.0 (2.0)*
Hyperactivity score	7.2 (2.5)**	6.8 (2.2)*	6.2 (2.5)*	7.4 (2.7)*	5.2 (2.5)*	5.3 (3.1)*
Peer problems	2.8 (1.9)	3.2 (2.4)*	2.4 (2.1)	3.9 (2.5)*	3.5 (1.9)*	3.8 (2.7)*
Total difficulties score	16.2 (6.4)**	16.2 (8.5)**	15.7 (6.3)*	18.5 (6.1)**	14.7 (5.8)*	15.0 (8.2)*
Prosocial score	6.7 (2.1)*	5.1 (3.4)**	7.8 (2.1)*	6.7 (3.0)**	7.7 (2.8)*	7.1 (2.7)*

* Above/below average. ** High/low.

Trauma studies hypothesize that preschoolers are more susceptible to distress and developmental problems following traumatic exposure, resultant in their limited cognitive capabilities when faced with a traumatic event [32,35,74]. Our results differ from these findings regarding PTSD symptomatology; however, the high prevalence of other psychiatric commodities witnesses some degree of distress. The trauma literature demonstrates high levels of comorbid psychopathology in children with PTSD and in children who have been exposed to traumatic events without developing PTSD compared to children with no exposure [75]. Although children with epilepsy may experience multiple adverse events during childhood, the associations between childhood-onset epilepsy and psychopathology are complex [6,7].

Additionally, the methodological approach to the preschool group should be considered. PTSD and comorbid psychiatric diagnoses were assessed by interviewing the parent, and parental proxy measures of child difficulties might be challenged on its accuracy [62,76,77]. Several PTSD symptoms are internalized, which means that the parent can have difficulties knowing if a child experiences symptoms or which experience is worse if the child has been exposed to more than one. Secondly, trauma-affected parents may assess their child's well-being through their own experiences

[78], affecting the accuracy of interpretation of the child's expressed behavior. These challenges may result in an underestimation of PTSD prevalence in this group of children.

Furthermore, it could be argued that limited cognitive abilities of preschoolers and children with more severe epilepsy, in general, can contribute to a lower level of PTSD symptoms since the children may not conceive the consequences of a situation that is perceived as potentially dangerous or can convey their symptoms [79]. Children with early-onset epilepsy tend to have more severe types of epilepsy and with greater risk of cognitive difficulties. In our study, children with PTSD symptomatology had a mean age of 7 years when diagnosed with epilepsy, whereas children with no symptoms had a mean age of 4. They had higher overall executive functioning, a shorter duration of epilepsy, and one out of three had focal or multifocal epilepsies. These results indicate that the children with symptoms of PTSD were better cognitively functioning and with less severe epilepsy than the children with no symptoms. However, children with PTSD symptoms did have more significant overall behavioral difficulties than children with no symptoms.

Our overall results for the group we could assess for PTSD symptomatology are somewhat adverse to the general findings on psychiatric comorbidity and behavioral difficulties in children with epilepsy [12,80,81]. Children with more complicated epilepsies are known to have higher levels of both compared to children with less complicated epilepsies. One reason for the adverse results for the PTSD group could be that the study includes children with more severe epilepsies only. A comprehensive comparison with children with uncomplicated epilepsies was not possible. However, the results could indicate that higher functioning children with severe epilepsy might better reflect on and express trauma symptoms.

Additionally, 40% of the children with symptoms of PTSD had a parent with psychopathology. Parental psychopathology could contribute to the high concurrency of trauma symptoms in children in the sense of secondary traumatization. Often, it is the parent and not the child that experiences their

child's seizures, evidently if it is generalized seizures and could be characterized as a traumatic event by its nature. The caregiver's emotional reaction to a seizure immediately related to the seizure or talking about the event in the distance to the seizure could result in a transference of distress to the child. Furthermore, many diverse events are related to severe childhood epilepsy than seizures characterized as traumatic and jointly experienced by the child and their parents. The parental emotional reactions to the collectively experienced traumatic events could further intensify the child's experience and emotional reactions. However, further research is needed to clarify how the child's experiences differ from the experience of their parents to distinguish between secondary traumatization and trauma reactions from direct exposure.

The children in the group that were not included in the PTSD assessment had overall lower levels of functioning. Although the applied measurement tools in this study could not access the more severely impacted children, awareness about trauma exposure and symptoms thereof should be of importance in the assessment of these children, too, as psychiatric comorbidities have shown to be strongly associated with long-term life quality for all levels of epilepsy severity [1].

5. Limitations

Our study has several limitations. The low sample size compromises the power of the study results, and combining three different age groups, yet using different measures of PTSD across the groups, further compromises this. The DIPA and Darryl interviews are based on measuring PTSD according to DSM-IV, and the ITQ questionnaire is based on ICD-11. Although the assessment tools are developmentally sensitive, which is a great strength, the different methodological approaches make it difficult to determine whether the differences across the age groups are due to the age differences or the differences in measurement tools. However, despite some evidence that ICD-11 may reduce diagnostic rates in trauma-exposed populations relative to DSM-5 [82,83], cohort studies find the same prevalence of PTSD across the DSM-IV/5 and ICD-11 when measuring the general

population [84]. Future studies could benefit from measuring by the DSM-5 or ICD-11 PTSD across all three age groups.

A further concern could be the questions of the arousal cluster in the Darryl and DIPA interviews. Three out of five areas are related to problems falling asleep, irritability, and hyperactivity. All three symptoms are known side effects of antiepileptic drugs or sequelae to seizure activity. However, the three symptoms are not included in the ITQ questionnaire, which could point to the benefit of the ICD-11 PTSD diagnosis as a future measure of PTSD symptoms in children with epilepsy.

The limitations of the parent-proxy measure of child difficulties and psychopathology in preschoolers have been mentioned above. However, in this study, the possible misinterpretation of the caregivers concerning trauma symptoms in their child might have contributed to a lower rate of trauma symptoms and not the reverse. The prevalence of trauma symptoms in older children is high, and children with early-onset epilepsies are most likely at even higher risk of being exposed to traumatic events during their childhood than children with later-onset epilepsies. Furthermore, the school children were asked about symptoms directly related to their epilepsy and not adverse events associated with epilepsy, such as accidents or bullying. This could have affected the prevalence rate in this age group.

Due to the self-report measure of trauma symptoms in schoolchildren and adolescents, only children with the capabilities to understand and answer the questionnaires were included in the study of PTSD symptomatology. This group of children is solely representative of the better functioning children within more complicated and severe epilepsies. Research on trauma exposure and reactions to exposure in children with more severe epilepsy and lower levels of cognitive functioning might be beneficial. However, it would demand a cautious approach acknowledging the complexity of the condition.

Lastly, we did not include the measure of functional impairment in the Darryl or ITQ tests, and as such, the tests cannot be used as definitive diagnostic tools. Therefore, symptoms of PTSD have been described as symptomatology and not a diagnosis of PTSD.

6. Conclusion

Trauma exposure in severe childhood epilepsy is high; however, to the authors' knowledge, trauma symptoms in children with more complicated epilepsies have not previously been assessed with standardized tests. This present cross-sectional study assessed 50 children with severe epilepsy in three different age groups (0–5 yrs., 6–12 yrs., and 13–18 yrs.). We found a high number of PTSD symptoms and subclinical symptoms in schoolchildren and adolescents. Twenty-two percent of the overall sample met the criteria for PTSD. The prevalence of symptoms increased with age (6%, 28%, and 40%, respectively). Despite a lower level of PTSD symptoms in the preschoolers, we found comorbid psychiatric symptoms in 81% of the children witnessing a high level of distress in this group. All three age groups had elevated behavioral difficulties, and 40% of the children with trauma symptoms had a parent with concurrent psychopathology. Although the sample size is limited and our methodology is weakened by comparing across age groups and measurement tools, these findings highlight the importance of assessing trauma exposure in children with more complicated epilepsies and how the child experience is affected thereof. The limitations emphasize the need for further studies with larger sample sizes and research into trauma symptoms in children with more severe epilepsy than those assessable with the included assessment tools. The trauma perspective in severe childhood epilepsy might shed further light on the complicated associations between the well-studied biological and contextual variables that affect the quality of life in children with epilepsy and enable better preventative treatment options for this group.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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We confirm that we have read the Journal's position on issues in ethical publication and affirm that this report is consistent with those guidelines.

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Appendix C: PhD paper III

Title: Self-control and coping responses are mediating factors between child behavior difficulties and parental stress and family impact in caregivers of children with severe epilepsy

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Keywords; Pediatric epilepsy**,** parental stress, coping, self-control, child behavior difficulties.

Highlights

- Sense of control is an essential factor in parental perceived stress and family impact
- Parental coping mechanisms should be investigated when determining support needs
- Decreased self-control and higher levels of emotional coping response eliminate the protective aspect of social support

Abstract

Objectives: To gain a better understanding of parental support needs by assessing parental individual psychological factors as mediating factors between child behavior difficulties and parental perceived stress and family impact of severe childhood epilepsy.

Methods: One-hundred and sixty two parents of children with severe epilepsy were enrolled in the survey during the hospitalization of their child at the Danish Epilepsy Center. Questionnaires targeted the impact on the family, coping style responses, sense of control, and the level of parental perceived stress.

Results: Serial mediation models demonstrated a mediating effect of self-control and emotional coping (EMCOP) response between child behavioral difficulties and both parental stress ($F(4, 127) = 56.371$, $p < 0.001$, $R^2 = 0.64$) and family impact ($F(3, 134) = 32.202$, $p < 0.001$, $R^2 = 0.42$). Low level of control was associated with a higher level of EMCOP response, and a high EMCOP response was associated with greater perceived stress and family impact. Social support ceased to be a protective factor for parental stress in the presence of decreased self-control and higher levels of EMCOP response.

Conclusion: Individual caregiver psychological factors influence the degree to which sequelae of epilepsy impact family life and perceived stress in parents. Coping interventions should direct awareness toward the life-control aspect, coping response styles, and illness-specific factors to ensure that appropriate support is provided. Maintaining parental resources is essential, and the parents' capacities to handle the child's behavioral difficulties should be considered.

1. Introduction

Caring for a child with a chronic and sometimes life-threatening disease such as severe childhood epilepsy engenders high levels of psychopathology and stress in caregivers [1–5]. The causes of this high impact might seem evident; however, the relationship between illness-related factors and the level of impact on caregivers is not always a direct association. Comorbidity, including behavioral problems, occurs frequently in childhood epilepsy [6–8], and it is suggested that child behavioral difficulties are predominantly related to parental stress rather than illness-related factors such as seizure frequency or type of diagnosis [2,9,10].

Parental stress may further challenge the sustainment of a positive parent–child relation [11–13], and more significant behavioral difficulties are seen in children where the caregiver–child relation is challenged [14,15]. Furthermore, the nature of epilepsy elicits unpredictable life situations for many families, and parents may experience a lower sense of control in their own lives. Impairment or loss of control is associated with higher levels of stress in western cultures [16], and it is well established that an impaired sense of control is linked with psychopathology [17,18]. The early construct of control orientation by Rotter [19] comprises a continuum of external and internal locus of control. External locus of control at one end of the continuum is the generalized belief that outside forces determine important life events more than the person herself does. This could be factors such as fate, luck, or the influence of powerful others. The powerful others with the ability to control the lives of parents to children with epilepsy would be such as policy makers who decide the treatment available for childhood epilepsy. It could be anyone responsible for treatment, or the people who assist the family to get the needed support at home or have impact on which institutional support the child may receive. At the opposite end of the continuum is the internal locus of control, which is the generalized belief of personal control over important life events with the option to act. Additionally,

according to the transactional theory by Lazarus et al. [20–22], the relationship between impaired locus of control and stress should be understood in the context of adaptive coping mechanisms.

The transactional theory suggests that situational characteristics determine the adaptability of a strategy and that no specific coping strategies are to be preferred a priori. Locus of control is viewed as subordinate to coping strategies; hence, locus of control should be linked with emotional influence via coping strategies. Lastly, social support appears to be an essential buffer for the influence of stressful situations on mental distress and physical illness [23,24]. We have previously shown an association between self-control, social support, and perceived stress in parents of children with severe epilepsy [2], which is in line with known resilience factors in parents of children with developmental disabilities [25].

The current study investigated the influence of parental psychological resources as mediating factors for the impact of severe childhood epilepsy on parental stress development and broadened this perspective into family life impact.

2. Methods

2.1. Participants

Parents of children diagnosed with epilepsy (aged 0–18 years) were approached for participation in the study when hospitalized with their child at the pediatric department of the only tertiary epilepsy center in Denmark—the Danish Epilepsy Centre, Filadelfia. Participants signed informed consent, and data handling guidelines from the Danish Data Protection Agency were followed. We excluded non-biological caregivers and parents who were not native Danish speakers. During the 12-month period of data collection, parents of 287 children were asked to complete the study survey.

Table 1: Characteristics of children with epilepsy and their caregivers

Children	
Number of patients (girls %)	140 (46)
Age, M (SD)	8.9 (4.56)
Years with epilepsy, M (SD)	4.0 (3.72)
Epileptic diagnosis, n (%)	
Epileptic encephalopathy	26 (19)
Focal/multifocal epilepsy	73 (52)
Idiopathic generalized epilepsy	20 (15)
ESES	21 (14)
Seizure frequency, n (%)	
Seizure-free	37 (30)
Daily seizures	42 (34)
Weekly or less often seizures	44 (36)
Caregivers, n (%)	
Number of parents (mothers %)	162 (77)
Both parents living together	117 (72)
Employed	106 (65)
Caregiver measures, M (SD)	
Perceived Stress	20.2 (8.5)
Impact on Family	36.7 (10.8)
Personal Strain	13.1 (4.8)
Familial/social impact	23.5 (6.7)
Coping Style	
RATCOP	29.0 (5.0)
EMCOP	26.4 (6.0)
DETCOP	12.0 (2.7)
AVCOP	19.6 (3.8)
Self-control	4.4 (3.1)

M = mean. SD = standard deviation. n = number. ESES = Electrical status epilepticus during slow-wave sleep. RATCOP = rational coping. EMCOP = emotional coping. DETCOP = detached coping. AVCOP = avoidant coping.

2.2 Measures

2.2.1. Family impact

The impact of epilepsy on the family was measured by the Impact on Family Scale (IFS) [26]. The original 24-item scale was explicitly designed to measure the impact of pediatric chronic illness on the family, measuring four distinct domains: personal strain, familial/social impact, financial impact, and mastery. A revised IFS scale with 15 of the original 24 items was later recommended for

measuring a single impact factor, showing good to excellent psychometric properties [27,28]. The scores are measured on a four-point Likert scale, where a low total score defines a high impact. In the current study, the 15-item scale was used as a single factor measure of the general impact on the family, and sub-analyses were performed on two of the original scales—personal strain and familial/social impact—due to the qualitative nature of the questions in these two scales.

2.2.2. Parental stress

The caregiver's level of perceived stress was measured with the10-item Perceived Stress Scale (PSS-10) [29]. This is a self-reported questionnaire that evaluates the degree to which individuals believe their lives have been unpredictable, uncontrollable, and overloaded during the previous month. A higher score resembles higher levels of perceived stress. The 10-item scale has proved superior to the original 14-item scale and has shown acceptable psychometric properties across various cultures and countries [30].

2.2.3. Parental resources

The Multi-dimensional Scale of Perceived Social Support (MSPSS) [31] and the Visual Analogue Scale of Self-control (VASSC) [19,32,33] were used to evaluate external and internal resources in caregivers, respectively. The MSPSS is a 12-item measure of perceived adequacy of social support from three sources: family, friends, and significant other. It is a seven-point Likert scale where higher scores equals higher levels of support. The subscales and the total scale have good internal reliability with Cronbach's alpha (α) levels between 0.81 and 0.94 [34]. The total scale was used in this present study. The VAS-SC consists of a 10-centimeter line anchored at each end by two opposing statements related to the experience of self-control. At the high end of the scale (to the right) is a statement of not controlling in what direction the responder's life is taking (low level of self-control). Hence, the higher the score, the lower the sense of control. The VAS scale measures have reliable psychometric properties compared to Likert-scale measures [35,36].

2.2.4. Parental coping

The Coping Style Questionnaire (CSQ) [37] is a 37-item, four point Likert scale measure of parental coping styles. A higher score represents a more pronounced response style. This questionnaire distinguishes between four different coping styles, each with acceptable internal consistency of the scales (Cronbach's alpha (α)): rational coping (RATCOP; α = 0.85), emotional coping (EMCOP; α = 0.74), avoidance coping (AVCOP; α = 0.69), and detached coping (DETCOP; α = 0.90) [38].

2.2.5. Child characteristics

The Strength and Difficulties Questionnaire for Parents (SDQ-P) [39] measured the child's level of difficulties and prosocial behavior. The SDQ is a widely used and reviewed 25-item questionnaire [40–42] and has national norms [43]. It includes five subscales: Emotional Symptoms, Conduct Problems, Hyperactivity, Peer Problems, and Prosocial Behavior. The total scale was used in this study as a proxy measure of the sequelae of childhood epilepsy. A higher total score approximates higher levels of behavior difficulties.

The caregiver provided diagnostic information concerning the child. A child neurologist reviewed the diagnostic information regarding epilepsy diagnosis and type of seizures for the purpose of categorized analyses matching the diagnostic criteria of the International League Against Epilepsy (ILAE) [44]. Epilepsy-related factors included the type of epilepsy, type and frequency of seizures, the child's age at seizure onset, and years with epilepsy.

Demographic information included gender and age (caregiver and child) and caregiver education, job situation, and marital status.

2.3. Statistical analysis

Quantitative statistics were analyzed using IBM SPSS version 24. All questionnaire variables were screened for missing data, and Little's MCAR test was performed. Missing values up to 20% at

item or case level were imputed using the expectation–maximization (EM) method. This method was run for each subdomain in composite scale measures (IFS, MSPSS, CSQ, SDQ-P). Summary statistics were calculated for child factors and sociodemographic factors. Possible predictive caregiver- and child-associated variables were first tested for their bivariate correlation with the caregiver's level of perceived stress and family impact. They were entered into the multivariable analyses if they were correlated at $p < 0.20$ or were identified a priori as being of interest based on previous research. The level of statistical significance was set at $p < 0.05$. Estimation of statistical power was assessed with the G*Power 3.1 [45]. To avert a potential clustering effect of parents included from the same household, we assessed all parental individual psychological factors and outcome measures (IFS, MSPSS, CSQ, VAS-SC) across same-gender co-admitted and single-admitted parents (ANOVA). No significant differences were found for any outcome measure. Grouping co-admitted and single-admitted parents irrespective of gender (two groups) did not reveal any significant differences either.

Hierarchical linear regression analyses were performed to assess a possible mediation effect of parental psychological factors (CSQ-P, VAS-SC) on caregiver-perceived stress (PSS-10) and family impact (IFS), respectively. Assumptions of residual normality, linearity, and homoscedasticity were assessed, and outliers were removed from the further analysis. Multicollinearity among the explanatory variables was assessed using the variance inflation factor (VIF). The PROCESS macro by Hayes [46] was used for mediation analyses.

3. Results

The survey was completed by 162 caregivers (of whom 125 were mothers and 37 fathers) aged 27–60 years (mean 39.8 years, SD 6.7) of 140 children with epilepsy, giving a response rate of 49%. Both parents of 22 children participated in the survey. The children had a mean age of 8.9 years (0–18 years; SD 4.6) and a mean duration of epilepsy of 4.03 years (SD 3.72) (Table 1). Children of

parents who declined to participate in the survey had a mean age of 9.3 (0–18 years; SD 4.4) and 43% were girls. Parent and child characteristics have been described in full previously [2].

3.1. Mediating factors of perceived stress

We demonstrated in a previous publication that social support, the child's difficulties, and self-control were significant predictors of the level of the caregiver's stress when controlling for demographic factors and child epilepsy variables [2]. In the current study, we added coping style into the regression analyses and found that EMCOP added significantly to the model. It appeared to mediate the impact of child difficulties on parental perceived stress, reducing the magnitude of the direct effect on perceived stress by 28% (β; 0.36 vs. 0.25). It further reduced the direct effect of self-control on perceived stress by 43% (β; 0.48 vs. 0.29 None of the other three coping styles (DETCOP, RATCOP, AVCOP) remained significant in further analyses beyond bivariate analyses (Table 2).

In a serial mediation model with self-control and EMCOP as mediating factors of perceived stress and controlling for social support as a confounding factor, both factors mediated the relationship between child difficulties and parental stress in serial; indirect = 0.05, *SE* 0.03, 95% CI [0.01, 0.11] (Fig. 1). With this mediating effect of self-control and EMCOP, social support no longer showed a significant effect on parental stress b = -0.07, $b(127)$ = -0.22, p = 0.827 (Table 3). Contrast analyses between indirect effects were non-significant.

Table 2. Bivariate correlations of coping style and parental impact factors

	Impact measures				
	PSS-10	IFS Total	IFS-PS	IFS-FS	VAS-SC
RATCOP	-0.360**	0.208**	0.199*	0.192*	-0.261**
EMCOP	0.762**	-0.579**	-0.610**	-0.496**	0.630**
DETCOP	-0.319**	0.207**	0.197*	0.193*	-0.245**
AVCOP	0.206*	-0.152	-0.176*	-0.118	0.314**

* $p < 0.05$; ** $p < 0.01$. RATCOP = rational coping. EMCOP = emotional coping. ETCOP = detached coping. AVCOP = avoidant coping. PSS-10 = perceived stress scale. IFS Total = impact on family scale total score. IFS-PS = impact on family scale personal strain score. IFS-FS = impact on family scale familial/social score. VAS-CS = self-control scale score.

3.2. The impact on family

The age at which the child was diagnosed with epilepsy, the nature of the seizures, and child difficulties were significant predictors of the overall impact on family life (Table 4). Generalized tonic-clonic seizures alone or with other types of seizures were significantly associated with family impact compared to seizure-free children or other types of seizures alone. The younger the child at diagnosis and the more difficulties parents considered their child to have at the time of the survey, the higher the impact on the family. The child factors remained significant when entering parental psychological factors into the regression analyses. Self-control and EMCOP style increased the explained variance of the model significantly ($\Delta R^2 = 0.131$) and decreased the direct effect of child difficulties on family impact with a total of 38 % (β; 0.45 vs. 0.29). A significant indirect effect was demonstrated in mediation analysis with self-control and EMCOP mediating between child difficulties and impact on the family (Fig. 2) for both mediators separately and in serial; indirect (completely standardized) = -0.05, *SE* 0.03, 95% CI [-0.12, -0.00] (Table 5).

When we repeated the analyses on the two IFS domains of personal strain and familial/social impact (suppl. Table A1), we found that self-control mediated the relationship between child difficulties and impact on both scales (familial/social; indirect = -0.10, *SE* = 0.04, 95% CI [-0.18, -0.08], personal strain; indirect = -0.07, *SE* = 0.03, 95% CI [-0.15, -0.02]) (suppl. Figure A and B). However, coping style remained significant only in predicting personal strain ($b = -0.04$, $t(135) = -4.34$, $p < 0.001$) (suppl. Table A2 and B) and mediated the relationship between child difficulties and personal strain together with self-control in serial mediation analyses, indirect = -0.06, *SE* 0.02, 95% CI [-0.10, -0.02]. All contrast analyses between indirect effects were non-significant.

Table 3. Model summary for the serial multiple mediator model for parental stress that is depicted in Figure 1

		M_1					M_2					Y			
		B	95%CI	*SE B*	*β*		*B*	95%CI	*SE B*	*β*		*B*	95%CI	*SE*	*β*
X (Child difficulties)	a_1	0. 091*	[.02, .17]	0.795	0.202	a_2	0.153**	[.05, .26]	0.053	0.194	*c*’	0.318***	[.18, .46]	0.072	0.264
M_1 (Self-control)		-	-	-		d_{21}	0.971***	[.74, 1.21]	0.119	0.552	b_1	0.622**	[.24, 1.00]	0.193	0.232
M_2 (Emotional coping)		-	-	-			-	-	-	-	b_2	0.741***	[.51, .97]	0.117	0.485
CoV (Social support, inv. sq. root)		0.574***	[.14, .91]	0.169	0.290		0.550*	[.08, 1.02]	0.237	0.158		-0.070	[-.70, .56]	0.319	-0.013
Constant	i_{M1}	0.351***	[-1.22, 1.92]	0.795		i_{M2}	11.230***	[9.18, 13.42]	1.072		i_y	-2.613	[-6.44, 1.21]	1.932	
		$R^2 = 0.163$					$R^2 = 0.513$					$R^2 = 0.640$			
		$F(2, 129) = 12.557$, $p < 0.001$					$F(3, 128) = 44.875$, $p < 0.001$					$F(4, 127) = 56.371$, $p < 0.001$			

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. M = mediator variable. CoV = covariate variable. B = unstandardized coefficient. CI = confidence interval. SE B = standard error of B. β = standardized coefficient.

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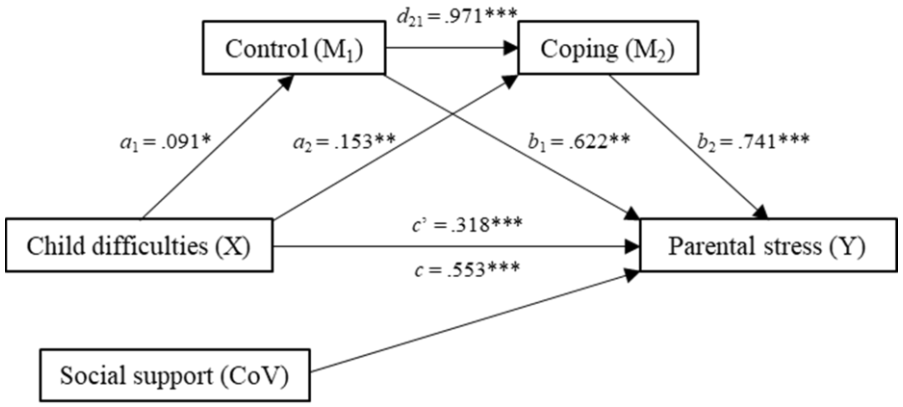


Figure 1. Statistical diagram of the serial multiple mediator model for parental stress

Table 4. Hierarchical regression analysis predicting family impact

	Model 1				Model 2				Model 3			
	B	*SE B*	*β*	*sr*	*B*	*SE B*	*β*	*sr*	*B*	*SE B*	*β*	*sr*
Constant	49.125**	3.848			53.871**	3.570			58.847**	4.031		
Age, child	-0.228	0.242	-0.091	-0.087	-0.254	0.217	-0.101	-0.108	-0.241	0.213	-0.096	-0.105
Age at diagnosis	0.925**	0.277	0.345	0.295	0.871**	0.249	0.324	0.308	0.826**	0.245	0.308	0.300
Diagnosis, EE	-2.538	3.134	-0.090	-0.075	-3.070	2.820	-0.109	-0.101	-4.017	2.785	-0.142	-0.133
Diagnosis, focal/multifocal	-4.725	2.421	-0.217	-0.178	-3.676	2.185	-0.169	-0.154	-3.926	2.141	-0.180	-0.169
Diagnosis, ESES	0.279	2.978	0.009	0.009	0.472	2.678	0.016	0.016	0.603	2.621	0.020	0.021
Seizure type, GTC/GTC+	-8.313**	2.442	-0.316	-0.300	-7.378**	2.202	-0.281	-0.297	-6.508**	2.184	-0.248	-0.268
Seizure type, other	-0.246	2.053	-0.011	-0.011	-0.639	1.847	-0.029	-0.032	-0.542	1.808	-0.025	-0.028
Child difficulties	-0.712**	0.113	-0.450	-0.503	-0.530**	0.107	-0.335	-0.417	-0.440**	0.111	-0.278	-0.346
Employed	2.681	1.916	0.110	0.128	-0.121	1.800	-0.005	-0.006	-0.038	1.762	-0.002	-0.002
Self-control					-1.334**	0.249	-0.380	-0.446	-0.943**	0.290	-0.269	-0.290
Emotional coping									-0.399*	0.161	-0.210	-0.225
	$R^2 = 0.453$ $F(9, 117) = 10.770$, $p < 0.001$				$R^2 = 0.562$, $\Delta R^2 = 0.109$ $\Delta F(1, 116) = 28.768$, $p < 0.001$				$R^2 = 0.584$, $\Delta R^2 = 0.022$ $\Delta F(1, 115) = 6.133$, $p = 0.015$			

* Uncorrected significance $p < 0.05$; ** Bonferroni corrected significance $p < 0.05$. EE = epileptic encephalopathy. ESES = electrical status epilepticus during slow-wave sleep. GTC/GTC+ = generalized tonic-clonic seizures alone or with other types of seizures. SE = standard error. B = beta. sr = partial correlation.

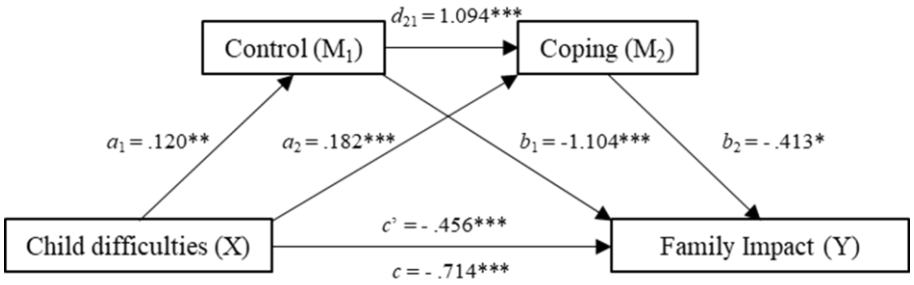


Figure 2. Statistical diagram of the serial multiple mediator model for family impact

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Table 5. Model summary for the serial multiple mediator model for family impact that is depicted in Figure 2

		M_1					M_2					Y			
		B	95%CI	*SE B*	*β*		*B*	95%CI	*SE B*	*β*		*B*	95%CI	*SE B*	*β*
X (Child difficulties)	a_1	0.120**	[.04, .19]	0.037	0.263	a_2	0.182***	[.08, .29]	0.053	0.223	c'	-0.456***	[-.68, -.24]	0.111	-0.292
M_1 (Self-control)		-	-	-	-	d_{21}	1.094***	[.86, 1.33]	0.119	0.595	b_1	-1.104***	[-1.71, -.50]	0.304	-0.316
M_2 (Emotional coping)		-	-	-	-		-	-	-	-	b_2	-0.413*	[-.75, -.07]	0.172	-0.217
Constant	i_{M1}	2.268***	[.99, 3.55]	0.647		i_{M2}	12.607***	[10.75, 14.46]	0.938		i_y	57.550***	[51.87, 63.23]	2.873	
			R^2 = 0.070 $F(1, 136)$ = 10.137, p = 0.002					R^2 = 0.473 $F(2, 135)$ = 60.604, p < 0.001					R^2 = 0.419 $F(3, 134)$ = 32.202, p < 0.001		

* p < 0.05; ** p < 0.01; *** p < 0.001. M = mediator variable. CoV = covariate variable. B = unstandardized coefficient. CI = confidence interval. SE B = standard error of B. β = standardized coefficient.

4. Discussion

The study results indicate that parental psychological factors influence the degree to which sequelae of epilepsy impact family life and the level of perceived stress in parents. The degree of child behavior difficulties impacts how parents experience being in control of their own lives. A lower level of control is associated with a higher level of EMCOP response, and a higher EMCOP response is associated with higher levels of perceived stress and family impact.

These findings diverge from a recent study on emotion-focused coping strategies and family burden in parents of children with epilepsy [47], where emotion-focused strategies were a protective factor for parental psychopathology. However, the authors assessed coping strategies using the widely used COPE questionnaire [48], which is linked to the dispositional perspective of coping mechanisms. The COPE questionnaire encompasses appraisal, humor, positive reinterpretation, and religious beliefs as active coping strategies. In contrast, our study's EMCOP response style (CSQ, EMCOP) encounters the feeling of being overwhelmed, sad, helpless, and isolated [21,37].

The theoretical understanding of coping mechanisms is broadly speaking divided into dispositional and contextual perspectives, or more explicitly, coping dispositions and coping responses [48]. The differences between instruments measuring dispositional or contextual coping mechanisms are essential to note when comparing findings across studies. It is most likely, however, that coping mechanisms operate in a combination of the two perspectives, emphasizing that individuals are active agents who can impact the outcomes of stressful life events and be shaped by them [49,50]. Collectively, the two perspectives indicate that parental stress results from the degree to which parents can handle the child's difficulties and is not merely a direct effect of the severity of the child's behavioral difficulties.

On a conceptual level, our study results correspond to the general literature about the mutual interaction of self-control and coping strategies when an individual is challenged by a stressful event

[20,22] and about parental coping related to childhood illnesses [10,51]. Although not significant after controlling for epilepsy-specific factors and self-control, the three other coping styles were significantly correlated with perceived stress in the bivariate analyses. Rational and detached coping were negatively correlated with stress, while avoidant coping (as with EMCOP) was positively correlated with stress. In a contextual perspective, a person adapts their coping response to different situations [22].

Our results indicate that rational and detached coping responses may act as protective factors toward parental stress, while both avoidant and EMCOP responses can cause higher levels of stress. Our results further indicate that parents who respond with a higher level of EMCOP to high levels of child difficulties and have lower self-control will experience higher stress levels and more impact on family life. Thus, in a preventive perspective, the knowledge of how caregivers respond to stressful events could help clinicians to predict potential higher levels of stress in parents and provide support accordingly to prevent further impact.

It is noteworthy that the protective factor of social support is no longer significant when lower levels of self-control and higher levels of EMCOP responses are present. This finding is contrary to most studies on the beneficial effects of social support [23] and emphasizes the importance of being aware of the combination of lower control and higher EMCOP response style. External resources do not seem to help lower the stressful impact of child difficulties on parental stress in these circumstances, and caregivers might need personalized support to handle the impact in a preventative way.

Further analyses of the two original domains of the Family Impact Scale (personal strain and familial/social impact) demonstrated that self-control was a mediating factor between child difficulties and both domains. However, EMCOP only mediated the relationships related to personal strain, not familial/social impact. The unpredictable nature of epilepsy (particularly severe childhood

epilepsy) is characterized by external and, to some extent, uncontrollable events such as daily seizures, frequent hospital visits, and emergency calls from the child's institutional setting or when out on visits with family or friends. Daily uncertainty influences long-term decisions as well. Planning for future activities and events such as vacations, school activities, social events, or job/educational-related changes is challenged by the daily care and the uncertainties related to illness prognosis.

These external unpredictable forces are actual events and are not merely related to a generalized belief regarding the degree to which one has personal control over important life events with options to act to maintain control. The events prevent families from engaging in social and leisure activities, regardless of which coping styles they use in the situation. The high risk of loss of self-control might be a specific aspect of childhood epilepsy compared to other childhood illnesses, and preventive interventions should include a specific awareness of this issue. However, studies on the effect of intervention approaches aimed at families with childhood epilepsy are still lacking [52–54].

Further research into how families could be helped in managing their experience of control loss would aid the development of intervention methods. Our study results indicate that generalized intervention methods might not be the optimal way to support all families. Individual characteristics of the caregivers should be considered alongside illness-specific factors in determining the support that is needed.

5. Limitations

Our response rate of 49% is somewhat low. Non-responders indicated that the emotional burden of dealing with the questionnaires, and to complete the extensive survey were too demanding while hospitalized with their child. This might indicate that part of the more burdened parents did not enter the study. Thus, our results might underestimate the impact of severe childhood epilepsy.

We used parent-completed questionnaires to assess child difficulties as a proxy measure of sequelae to childhood epilepsy. When assessing a child's maladaptive behavior in a clinical setting,

it is recommended to have two respondents in different settings to assess the child's behavior, as cross-informant consistency has shown to be somewhat low for the SDQ scale [42]. In our study, however, we were interested in how parents are impacted by their child's behavior difficulties and not whether their behavior was of clinical concern. Furthermore, the parents provided the epilepsy-related data. These proxy-report data are likely to be more sensitive to subjective understandings; however, a pediatric neurologist reviewed the diagnostic information for any adaption needed to the current diagnostic criteria developed by the ILAE [44].

6. Conclusion

Individual caregiver psychological factors influence the degree to which the sequelae of epilepsy impacts family life and perceived stress in parents. Child behavioral difficulties predict how parents experience the level of control they have of their lives, which further affects parental coping responses. Caregiver psychological factors act as mediators between child behavioral difficulties and the impact on both parents and familial. Therefore, coping interventions for families with childhood epilepsy should direct awareness toward the life-control aspect, alongside illness-specific factors, to determine the support that is needed. This support should be aimed at maintaining parental resources and take into account the parents' capacities to handle the child's behavioral difficulties.

7. Note

We confirm that we have read the Journal's position on issues in ethical publication and affirm that this report is consistent with those guidelines.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary material

Table A1. Hierarchical regression analysis predicting parental personal impact (IFS)

	Model 1				Model 2				Model 3			
	B	*SE B*	*β*	*sr*	*B*	*SE B*	*β*	*sr*	*B*	*SE B*	*β*	*sr*
Constant	4.252**	0.238			4.562**	0.217			4.963**	0.240		
Age, child	-0.013	0.015	-0.085	-0.078	-0.014	0.013	-0.097	-0.100	-0.013	0.013	-0.089	-0.097
Age at diagnosis	0.054**	0.017	0.344	0.282	0.051**	0.015	0.321	0.297	0.047**	0.015	0.299	0.289
Diagnosis, EE	-0.097	0.194	-0.058	-0.046	-0.131	0.172	-0.079	-0.071	-0.208	0.166	-0.125	-0.116
Diagnosis, focal/multifocal	-0.282	0.150	-0.220	-0.172	-0.214	0.133	-0.166	-0.148	-0.234	0.128	-0.182	-0.168
Diagnosis, ESES	0.027	0.184	0.015	0.013	0.039	0.163	0.022	0.022	0.050	0.156	0.028	0.030
Seizure type, GTC/GTC+	-0.506**	0.151	-0.327	-0.296	-0.445**	0.134	-0.287	-0.295	-0.375*	0.130	-0.242	-0.259
Seizure type, other	-0.060	0.127	-0.046	-0.044	-0.086	0.113	-0.066	-0.071	-0.078	0.108	-0.060	-0.067
Child difficulties	-0.037**	0.007	-0.401	-0.444	-0.026**	0.007	-0.273	-0.341	-0.018*	0.007	-0.195	-0.249
Employed	0.144	0.118	0.100	0.112	-0.039	0.110	-0.027	-0.033	-0.032	0.105	-0.022	-0.028
Self-control					-0.087**	0.015	-0.420	-0.471	-0.055**	0.017	-0.268	-0.287
Emotional coping									-0.032**	0.010	-0.287	-0.298
	$R^2 = 0.400$ $F(9, 117) = 8.655$, $p < 0.001$				$R^2 = 0.533$, $\Delta R^2 = 0.133$ $\Delta F(1, 116) = 32.987$, $p < 0.001$				$R^2 = 0.574$, $\Delta R^2 = 0.042$ $\Delta F(1, 115) = 11.236$, $p = 0.001$			

* Uncorrected significance $p < 0.05$; ** Bonferroni corrected significance $p < 0.05$. EE = epileptic encephalopathy. ESES = electrical status epilepticus during slow-wave sleep. GTC/GTC+ = generalized tonic-clonic seizures alone or with other types of seizures. SE = standard error. B = beta. sr = partial correlation.

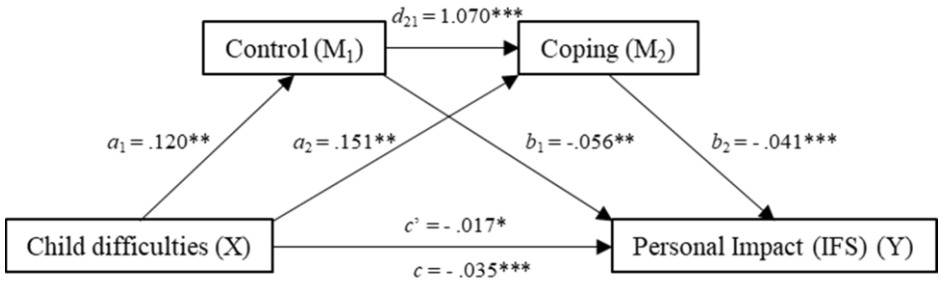


Figure A. Statistical diagram of the serial multiple mediator model for parental personal impact (IFS)

Table A2. Model summary for the serial multiple mediator model for parental personal impact (IFS) that is depicted in Figure A.

		M_1					M_2					Y			
		B	95%CI	*SE B*	*β*		*B*	95%CI	*SE B*	*β*		*B*	95%CI	*SE B*	*β*
X (Child difficulties)	a_1	0.120**	[.05, .19]	0.037	0.270	a_2	0.151**	[.04, .26]	0.057	0.181	c'	-0.017*	[-.03, -.00]	0.064	-0.179
M_1 (Self-control)		-	-	-	-	d_{21}	1.070***	[.82, 1.33]	0.129	0.568	b_1	-0.056**	[-.09, -.02]	0.017	-0.269
M_2 (Emotional coping)		-	-	-	-		-	-	-	-	b_2	-0.041***	[-.06, -.02]	0.009	-0.367
Constant	i_{M1}	2.221	[.96, 3.48]	0.637		i_{M2}	13.355***	[11.37, 15.34]	1.002		i_y	4.908***	[4.58, 5.24]	0.166	
		$R^2 = 0.073$ $F(1, 137) = 10.793$, $p = 0.001$					$R^2 = 0.411$ $F(2, 136) = 47.443$, $p < 0.001$					$R^2 = 0.431$ $F(3, 135) = 34.076$, $p < 0.001$			

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. M = mediator variable. B = unstandardized coefficient. CI = confidence interval. SE B = standard error of B. β = standardized coefficient.

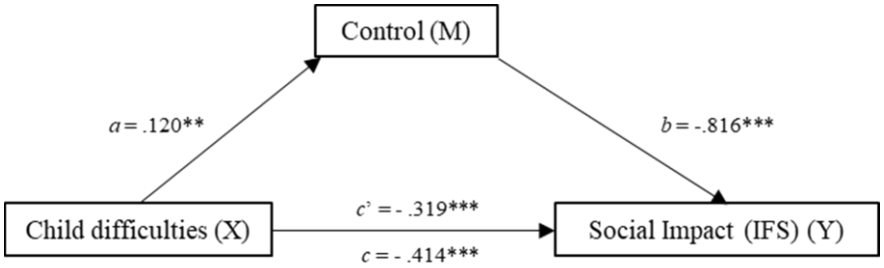


Figure B. Statistical diagram of the serial multiple mediator model for social impact (IFS)

Table B. Model summary for the mediator model for social impact (IFS) that is depicted in Figure B

		M_1					Y			
		B	95%CI	*SE B*	*β*		*B*	95%CI	*SE B*	*β*
X (Child difficulties)	*a*	0.120**	[.05, .19]	0.063	0.264	*c'*	-0.319***	[-.46, -.18]	0.070	-0.331
M_1 (Self-control)		-	-	-	-	*b*	-0.816***	[-1.13, -.50]	0.158	-0.377
Constant	i_M	2.220**	[.96, 3.48]	0.636		i_y	31.501***	[30.06, 34.94]	1.235	
		$R^2 = 0.070$ $F(1, 139) = 10.438$, $p = 0.002$					$R^2 = 0.318$ $F(2, 138) = 32.155$, $p < 0.001$			

** $p < 0.01$; *** $p < 0.001$. M = mediator variable. B = unstandardized coefficient. CI = confidence interval. SE B = standard error of B. β = standardized coefficient.

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Appendix D: Erratum

ERRATUM: The impact of severe pediatric epilepsy on experienced stress and psychopathology in parents

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The ITQ scale used to investigate post-traumatic stress disorder (PTSD) and complex PTSD (CPTSD) has been under substantial revisions since the data collection of this study. The final version is a 12-item measure for assessing the ICD-11 criterion for PTSD and complex PTSD (CPTSD) [1]. The new 12-item version was used when working with data for a later publication, and a syntax error in the algorithm for calculating PTSD in the published manuscript was found during the process of rerunning the analyses. Thus, analyses using the 12-item version with a corrected syntax demonstrate a higher prevalence of PTSD and CPTSD than demonstrated in the original manuscript. Thirty-three percent of parents showed symptoms of PTSD, and an additional 13% had symptoms of CPTSD. Fifty percent had concurrent symptoms of depression, and 33% had coexisting anxiety.

In total, 54% of parents showed symptoms of psychopathology by fulfilling the criteria for one or more diagnoses, and an additional 16% showed symptoms of sub-clinical PTSD alone.

The increased prevalence of PTSD and CPTSD did not significantly change any other leading associations; however, parents of children with idiopathic generalized epilepsy (IGE) had the exact prevalence of PTSD as parents of children with ESES (50% and 55%, respectively). Furthermore, marital status deceased to be significantly associated with PTSD.

There were no statistically significant differences in the caregiver's gender concerning PTSD or CPTSD symptomatology. Caregivers without current employment displayed a higher level of PTSD (χ^2 (1) = 8.759, p = 0.003) than caregivers having a part-time or full-time job. Parents with more than five years of education after primary school showed a significantly lower prevalence of PTSD (χ^2 (1) = 7.706, p = 0.006) (Table 2a).

Parent-rated child difficulties (SDQ) were significantly associated with symptoms of psychopathology compared to parents without symptoms. The mean difference (M_{diff}) for PTSD was 3.25, 95% CI [0.77, 5.72], t(115) = -2.594, p = 0.011, d = 0.48; where more difficulties were associated with higher prevalence of PTSD.

No other child-related factors or epilepsy-specific factors were individually significantly associated with PTSD (Table 2a+b) However, there was a relatively higher representation of caregivers with symptoms of PTSD to children with CSWS (continuous spike and wave during slow-wave sleep) and idiopathic generalized epilepsy (IGE) (51 % and 50% respectively) than other types of epilepsy. Fifty-five percent of caregivers of children with daily seizures showed symptoms of PTSD compared to 38% of caregivers of seizure-free children and 40% of caregivers to children with weekly or less frequent seizures.

Table 2a: Sociodemographic Features of Parents with or without PTSD/CPTSD (n = 132)

	Total sample	PTSD/CPTSD	No PTSD	*p*
Mother, *n* (%)	103 (78)	49 (82)	54 (75)	0.357
Divorced or living alone *n* (%)	34[a] (26)	18 (31)	16 (23)	0.326
Unemployed *n* (%)	44[b] (34)	28 (48)	16 (23)	0.003
< 5 yrs. professional education	81[a] (61)	44 (76)	37 (52)	0.006

[a]n =129, [b]n=127

Table 2b: Child Variables for Parents with or without PTSD/CPTSD (n = 132)

	Total sample	PTSD/CPTSD	No PTSD	*p*
Child psychiatric diagnosis, *n* (%)	13 (10)	6 (10)	7 (10)	0.927
Free from seizures, *n* (%)	37[c] (32)	14 (26)	23 (36)	0.256
ESES/CSWS, *n* (%)	20 (15)	8 (18)	9 (13)	0.762
Status epilepticus, *n* (%)	37[d] (30)	22 (38)	15 (22)	0.045

[c]*n=115,* [d]*n=127*

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