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The impact of early life seizures on cognitive development

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RÉSUMÉ

Il est connu que les déficits cognitifs sont une des comorbidités fréquentes des syndromes épileptiques de l'enfance à l'âge adulte. Ces déficits portent une atteinte significative au fonctionnement et à la qualité de vie des patients affectés. Ils sont typiquement reliés à l'étiologie, à l'âge à la première crise, au traitement par anticonvulsants ainsi qu'à la sévérité, durée, et type de crise. Cependant, la littérature livre des résultats plutôt divergents quant aux séquelles d'une convulsion isolée.

Suite à un épisode de status épilepticus (SE) chez l'enfant, reconnu comme étant le type de convulsion le plus sévère puisque les symptômes persistent pour une durée d'au moins 30 minutes, la littérature démontre des changements physiologiques significatifs qui sont reliés à des déficits cognitifs à long terme, notamment au niveau du développement, de l'intelligence globale, des capacités d'apprentissage et des fonctions exécutives. L'étude des troubles reliés au SE permet de soulever les séquelles qui pourraient être attribuées à des convulsions moins sévères, telles les convulsions fébriles (CF), le type de convulsions le plus fréquemment rencontré chez l'enfant pour lesquelles les séquelles cognitives demeurent peu connues. Il y a plusieurs types de CF (simple et complexe) et elles sont dans l'ensemble caractérisées par une crise survenant dans un contexte de fièvre en l'absence d'une infection du SNC. Bien que des changements physiologiques à la suite des CF plus sévères aient souvent été démontrés, les conséquences de ces convulsions sur la cognition sont peu étudiées et les résultats demeurent controversés. Quelques études ont porté sur l'impact des formes de CF les plus sévères sur les trajectoires développementales immédiatement suivant la convulsion et plusieurs études démontrent une intelligence globale normale plus tard dans la vie. Cependant, l'étude

standardisée, spécifique et objective mesurant l'évolution du développement de la petite enfance à l'âge scolaire n'a pas encore été effectuée.

Cette thèse comporte deux objectifs principaux. Le premier objectif était de comprendre les déficits cognitifs suite à un épisode de SE à travers une revue de la littérature (Article 1). Le deuxième objectif était d'étudier le développement cognitif suite à une CF complexe de l'apparition de la convulsion jusqu'à l'âge scolaire, dans le contexte de facteurs de risques connus pour un développement moins favorable (Article 2). Plus précisément, nous avons investigué le développement à l'intérieur de la première année suivant la convulsion (Article 2, *Infant Cohort*). De plus, nous avons étudié le développement cognitif des enfants de 5 à 6 ans ayant une histoire de CF, afin d'évaluer les fonctions cognitives plus complexes de manière spécifique et standardisée. Nous avons évalué l'apprentissage, la mémoire, et les fonctions exécutives (Article 2, *School-Age Cohort*).

Les résultats de l'étude clinique (Article 2) ont démontré un développement cognitif demeurant dans la norme à l'intérieur de la première année suivant l'apparition de la convulsion, sans impact de la durée de la crise ou de l'âge à l'apparition de la crise. À l'âge scolaire, les résultats ont démontré que intelligence globale n'est pas affectée suite à une CF complexe. Par contre, des différences de groupes significatives ont indiqué des difficultés cognitives spécifiques, particulièrement au niveau des fonctions exécutives, de l'apprentissage et de la mémoire, qui s'aggravent en fonction de la durée de la convulsion. Des difficultés émotionnelles ont également été démontrées chez les enfants ayant subi une CF complexe,

particulièrement au niveau du perfectionism. Ces difficultés étaient modulées par l'âge au moment de la crise.

L’ensemble de ces résultats démontre que, bien que le développement ne soit pas altéré dans la première année suivant une CF complexe, des séquelles cognitives sont apparentes à l’âge scolaire, caractérisées par des faiblesses significatives au niveau des fonctions exécutives, de l'apprentissage et de la mémoire. De façon générale, les résultats obtenus démontrent que les CF complexes peuvent affecter le développement de fonctions cognitives spécifiques, bien qu’à un degré moindre que ceux observés à la suite d'un SE. Il faudra plus de recherche pour approfondir notre compréhension de la nature hétérogène des CF et de leur impact sur le fonctionnement et la qualité de vie des enfants affectés.

Mots-Clés: Convulsions fébriles, status épilepticus, convulsion fébrile complexe, cognition, comportement, émotion, développement, fonctions exécutives, neuropsychologie, enfant

ABSTRACT

Cognitive impairment has consistently been shown to be a common comorbidity of epileptic syndromes throughout the lifespan, typically in relation to etiology, age at onset, treatment and seizure type, severity and duration, and significantly impacting function and quality of life in affected patients. However, evidence related to the impact of seizure events occurring in isolation, without defining or being part of any broader syndrome has been equivocal.

Evidence supports significant physiological alterations following early-life status epilepticus (SE), arguably the most severe form of seizure as symptoms persist for at least 30 minutes, which has further been linked to long-term cognitive residua related to altered development, global intelligence, learning capacities and executive function, particularly as they occur in the developing brain. Understanding cognitive outcome following SE events can orient our understanding of the impact of less severe forms of seizures on the developing brain, namely febrile seizures. Febrile seizures (FS), which represent a group of seizures (i.e., simple and complex types) that occur in association with a febrile illness in the absence of a CNS infection, are the most common form of childhood seizure, for which cognitive outcome remains unclear. Although physiological alterations have been shown, particularly but not exclusively in the most severe forms of FS, cognitive and behavioral outcome has been understudied to date and remains controversial. Few studies have investigated the impact of development immediately following the most severe form of FS, and evidence demonstrates unaltered global intelligence in later life. However, the evolution of the impact of FS on cognitive development from infancy into childhood using standardized, specific and objective measures has yet to be studied.

The general objectives of the current thesis were two-fold. The first objective was to understand cognitive outcome following SE through a review of the literature (Article 1). The second objective was to investigate development and cognition following an initial complex FS from onset to school-age, in the context of known risk factors for poor outcome, including all types of complex features (Article 2). More specifically, we aimed to study development within the first year-post onset (Article 2, Infant Cohort). Furthermore, we aimed to examine cognitive development in a cohort of children old enough for cognitive functions to be sufficiently differentiated (i.e., school-age) to allow specific, objective and standardized assessment of the impact of different complex features on specific functions, particularly related to learning/memory and executive function (Article 2, School-age cohort).

Results of the clinical investigation revealed normal cognitive and behavioral development within the first year-post complex FS onset as compared to controls, without impact of seizure duration or age at seizure onset. At school-age, results revealed unaltered global intelligence following early-life complex FS. Significant group differences however indicated difficulties in specific cognitive domains, including executive functioning, and to a lesser extent, learning and memory in these children, as a function of seizure duration. Emotional challenges, particularly perfectionism, were further noted in children having suffered complex FS, as a function of precocity of seizure onset.

Taken together, our findings demonstrate that although development was unaltered following early-life FS, cognitive sequelae are apparent at school-age, characterized by challenges in

executive functioning and learning/memory. Overall, the current results support the hypothesis that complex FS, even without meeting criteria for FSE, may affect the development of specific cognitive functions, although to a lesser extent than those observed following SE. Future research is nevertheless required to better understand the heterogeneous nature of FS, as well as their outcome and impact on quality of life.

Key words: Febrile seizures, status epilepticus, complex febrile seizure, cognition, behavior, emotion, development, executive function, neuropsychology, children

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LIST OF ACRONYMS

ADHD: Attention Deficit Hyperactivity Disorder

AED: Antiepileptic drugs (treatment)

CBCL: Child Behavior Checklist

CNS: Central Nervous System

CVLT-C: California Verbal Learning Test for Children

DSM: Diagnostic and Statistical Manual of Mental Disorders

EEG: Electroencephalography

ER: Emergency Room

FEBSTAT: The "Consequences of Prolonged Febrile Seizures in Childhood" study

FS: Febrile Seizure

FSE: Febrile Status Epilepticus

GABAa: Gamma-Aminobutyric Acid receptor A

GEFS+: Generalized Epilepsy with Febrile Seizures plus

ILAE: International League Against Epilepsy

IQ: Intellectual Quotient

MRI: Magnetic Resonance Imaging

NEPSY-II: Developmental Neuropsychological Assessment, 2nd Edition

NCPP: National Collaborative Perinatal Project

sAHP: slow afterhyperpolarization

SE: Status Epilepticus

TLE: Temporal Lobe Epilepsy

WAIS-R: Wechsler Adult Intelligence Scale, Revised

WPPSI-III: Wechsler Preschool and Primary Scale of Intelligence, 3rd Edition

LIST OF ABBREVIATIONS

Bayley-III: Bayley Scales of Infant and Toddler Development, 3rd Edition

e.g.: exempli gratia (for example)

et. al.: et alii (and colleagues)

i.e.: id est (in other words)

Knowledge comes, but wisdom lingers.

Alfred Lord Tennyson

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INTRODUCTION

Epilepsy encompasses a group of neurological illnesses characterized by epileptic seizures, which are due to abnormal excessive or synchronous electrical activity in the brain (Moorthy et al., 2018). Cognitive impairment is a common comorbidity of epilepsy, which further impacts functioning and quality of life. The most prominent cognitive difficulties observed in this population are memory impairments, mental slowing and attentional difficulties (Aldenkamo, 2006). It has been argued that the cognitive deficits observed largely depend on the pathophysiology of the seizure disorder per se, such that patients suffering from temporal lobe epilepsy are at higher risk of presenting memory impairments, patients suffering from frontal lobe epilepsy are at higher risk of presenting executive impairments, and those with altered thalamo-cortical networks are at higher risk of language and executive functioning impairments (Moorthy et al., 2018). The etiologies of cognitive deficits in epilepsy are multifactorial. Early age at seizure onset has been argued to be the best predictor of cognitive outcome, although several other risk factors have been identified, including seizure type and severity, seizure duration, and use of antiepileptic medication (Strauss, 1995; Aldenkamo, 2006). Cognitive impairments in the context of epileptic disorders are generally considered lasting, particularly when seizure occurrences begin at younger ages (Moorthy et al., 2018).

In considering the pediatric population more specifically, epileptic encephalopathies together form a group of conditions in which epileptic electrical discharges are associated with progressive cerebral dysfunction in the developing brain (Dulac, 2001; Khan & Baradie, 2012). The International League Against Epilepsy (ILAE) has recognized eight age-related

syndromes under the rubric of "epileptic encephalopathies": early myoclonic encephalopathy and Ohtahara syndrome during the neonatal period, West syndrome and Dravet syndrome during infancy and myoclonic status in nonprogressive encephalopathies, Lennox-Gastaut syndrome, Landau-Kleffner syndrome and epilepsy with continuous spike waves during slow wave sleep during childhood (Engel, 2001). These syndromes are commonly characterized by severe and aggressive epileptogenic activity as manifested through EEG paroxysmal activity; seizures that are multiform and intractable, cognitive, behavioral and neurological deficits, as well as occasional early death (Yamatogi & Ohtahara, 1981; Donat, 1992; Dulac, 2001; Michael & Thomas, 2003). In particular, the EEG characteristics of epileptic discharges measured in each syndrome are age-related and vary according to the stage of brain maturity at the time the seizures occur (Yamatogi & Ohtahara, 1981; Donat, 1992; Khan & Baradie, 2012). Specifically, EEG primarily demonstrates burst-suppression patterns in the neonatal period, progressing to hypsarrhythmia in infancy and slow generalized spike-wave discharges in childhood (Yamatogi & Ohtahara, 1981; Dulac, 2001). With increasing age, seizure and epileptogenic features will evolve from one stage to another, and evolutional changes from Ohtahara syndrome to West syndrome to Lennox-Gastaut syndrome are frequently observed with age (Donat, 1992; Michael & Thomas, 2003). Although epileptic encephalopathies are known to attenuate or even stop in adolescence and adulthood, persistent residual neurocognitive sequelae have been well documented (Yamatogi & Ohtahara, 1981; Michael & Thomas, 2003; Khan & Baradie, 2012). Developmental trajectories have been observed to be stunted in all syndromes, including significant psychomotor delays and deficits, as well as mental and cognitive retardation (Khan & Baradie, 2012). Language deficits have been well documented following Dravet syndrome and Landau-Kleffner syndrome. Learning difficulties

have been noted following Ohtahara syndrome. Frontal lobe deficits, including difficulties with judgment and the ability to control and anticipate behavior, have been observed in epilepsy with continuous spike waves during slow wave sleep (Michael & Thomas, 2003; Khan & Baradie, 2012).

A constellation of several different clinical presentations commonly occurs in epileptic encephalopathies, including atonic seizures, astatic seizures, clonic seizures, epileptic spasms, myoclonic seizures, myoclonic-atonic seizures and tonic seizures (Khan & Baradie, 2012). When any of these symptoms occur for a duration longer than 30 minutes, the semiology is consistent with status epilepticus (SE), which is considered the most extreme and severe form of a seizure (Trinka, et al., 2015). Moreover, when any of the symptoms occur as a result of a febrile illness rather than a neurological condition, the semiology is consistent with febrile seizures (FS), the most common form of childhood seizure (Shinnar & Glauser, 2002). SE and FS may occur as an isolated seizure event without defining or being part of any broader syndrome. Although epileptic encephalopathies have been strongly and consistently associated with persistent long-term cognitive sequelae (Michael & Thomas, 2003; Khan & Baradie, 2012), and isolated SE events have generally been shown to impact cognitive development (Sheppard & Lippé, 2012), much less is known about the impact of isolated FS events on cognition. Even though it is a significantly less severe form of seizure, it is the most commonly occurring one, and more research is required to better understand its impact on the developing brain and cognitive development.

STATUS EPILEPTICUS

Status Epilepticus (SE) is the most severe form of a seizure. It's a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain (Trinka, et al., 2015). According to its updated ILAE definition, "SE is a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms which lead to abnormally prolonged seizures" (ILAE, 2015). It is agreed that the seizure in question must persist for at least 30 minutes in order to meet criteria for SE, given that irreversible neuronal injury typically occurs after this length of time. Indeed, it is a condition that can have long-term physiological consequences, including neuronal injury, neuronal death and alterations of neuronal networks (ILAE, 2015). SE can either be classified as convulsive (i.e., with prominent motor symptoms and impairment of consciousness) or non-convulsive (i.e., without motor symptoms or impairment of consciousness), and EEG patterns are non-specific (Lowenstain, et al., 1998). It is not a disease entity, but rather an event with many different etiologies. At least half of patients presenting with SE do not suffer from any particular syndrome or epilepsy, rather the event is due to acute or remote central nervous system (CNS), or systemic illness (Maytal, et al., 1989). Although SE can occur at any age, 40% of SE events occur prior to 2 years of age, owing to the volume of neurons and excitatory connections prior to functional specialization, argued to create an imbalance between excitatory and inhibitory connections, which increases the immature brain's vulnerability to hypersynchronization and SE (Shinnar, et al., 1997; Wasterlain, et al., 1993; Scott, et al., 1998). Febrile SE (FSE) is the most common etiology in children, in which high fever without any other provocation to the CNS induces the SE event (Fountain, 2000).

Cognitive sequelae following SE

Residual cognitive sequelae following SE in early life have been relatively well documented. Alterations in global intelligence, verbal and non-verbal intelligence and motor development have been demonstrated following early-life episodes lasting longer than one hour (Kolfen, et al., 1998; Dam, 1990; Van Esch, et al., 1996, Aicardi & Chevrie, 1970). More specifically, it has been argued that the age at which the SE event occurs will hinder the cognitive abilities under development at the time. Roy, et al. (2011) demonstrated that when an FSE event occurred prior to 11 months of age, hand-eye coordination and motor ability were most affected, but spared in children with FSE onset beyond 12 months of age, who in turn manifested difficulties in language and social behavior. When tested at 2 years of age, these children presented shortcomings in executive functioning, including self-monitoring and inhibition difficulties. Although age at onset is argued to be a principal predictor of subsequent cognitive sequelae, duration and frequency of seizures, as well as etiology are also important risk factors.

Taken together, cognitive sequelae following SE, the most severe form of seizure, has been relatively well documented (Sheppard & Lippé, 2012). Understanding the impact of early life SE and FSE on cognitive development can begin to shed light on understanding cognitive sequelae following early life seizures that are less severe in nature, although the most common, namely, Febrile seizures (FS).

FEBRILE SEIZURES

Definition

Febrile Seizures (FS) are the most common form of childhood seizure disorder. The International League Against Epilepsy (ILAE) defines a FS as "a seizure in association with a febrile illness in the absence of a CNS infection or acute electrolyte imbalance in children older than 1 month of age without prior afebrile seizures" (ILAE, 1993; Engel, 2006; Patel, et al., 2017). Since fever is associated with seizure in FS, neurological illness such as meningitis, encephalitis, and others must be excluded upon evaluation. Febrile Seizures usually occur within the first 24 hours of an illness, and fever typically reaches temperatures of 38^0C or higher (Leung & Robson, 2007; Berg & Shinnar, 1996). With regards to semiology, FS are mostly generalized and convulsive (i.e., generalized tonic-clonic seizures), however approximately 5% present with non-convulsive features, including unconsciousness, staring, eye deviation and atonia. (Pavlidou, 2013; Patel, et al., 2015).

Classification

Febrile Seizures are classified as either simple or complex based on the duration and recurrence of the seizure, as well as the presence of focal features (ILAE, 1993; Shinnar & Glauser, 2002). Simple FS is characterized by an isolated, brief (fewer than 10 minutes) and generalized seizure, whereas complex FS is more severe and quite heterogeneous in its presentation. It is characterized by either focal onset, prolonged duration (lasting between 15 and 30 minutes), occurring more than once during febrile illness, or a combination of different complex features. Febrile status epilepticus (FSE) is the most severe type of complex FS in which the seizure persists for at least 30 minutes. Although research has consistently

demonstrated benign outcomes following the occurrence of a simple FS, such that the affected children have been shown to develop similarly to otherwise healthy children who have not suffered seizures (Chang et al., 2000, Berg & Shinnar, 1996), evidence related to outcomes following complex FS remains unclear and controversial.

Epidemiology

Febrile Seizures occur in 2% to 5% of children between the ages of six months and five years (Verity et al., 1985; Shinnar & Glauser, 2002; Pavlidou, et al., 2013). Epidemiological studies demonstrate that FS onset peaks at 18 months and that onset beyond the age of six is rare (Leung & Robson, 1991; Baumann, et al., 2000). The incidence has been documented to be slightly higher in boys than girls (male to female ratio 1.1:1 to 2:1), although some studies do not show any sex differences (Pavlidou, 2013; Stafstrom, 2002; Chung, 2014). In affected children, approximately 75% will suffer simple FS and 20% to 30% will suffer complex FS (Annegers, et al., 1987; Shinnar & Glauser, 2002; Patel, 2017). The national collaborative perinatal project (NCPP), a study that prospectively followed 1706 children having suffered FS from birth to 7 years of age, revealed that 28% of children presented with an initial complex FS, of which 4% were focal, 7.6% were prolonged and 16.2% were recurrent (Capovilla, et al., 2009). Febrile status epilepticus accounts for 5% of FS events and 25% of overall SE events in children (Berg & Shinnar, 1996; Maytal & Shinnar, 1990; Patel, et al., 2017). Early results of the FEBSTAT study, a prospective and longitudinal multi-center study investigating the long-term impact of FSE on cerebral and cognitive development, reveal that it's presentation is focal in 67% of cases, and its onset peaks in relatively younger children (median age of 1.3 years) (Shinnar, et al., 2008). Moreover, although a seizure lasting at least

30 minutes is required to meet FSE criteria, the FEBSTAT study revealed a median seizure duration of 68 minutes and 24% of durations lasting more than two hours.

Etiology

As per their definition, FS are induced by a fever of at least 38^0C, typically associated with a systemic illness. The age-specific mechanisms involved in seizure development related to high fever are however quite debated and overall suggest multifactorial etiologies, including both environmental (including the systemic illness and fever itself) and genetic factors (Offringa, et al., 1994; Berg, et al., 1999; Audenaert, et al., 2006).

The pathogenesis of FS remains unclear and has mostly been studied through animal models. Given that FS are age-dependent, there seems to be a temporal association between the immature CNS and the onset of FS, although this association has yet to be clearly established, a situation which is further complicated by the heterogeneity of FS presentations. It is suggested that fever arising from febrile illness is linked to an imbalance between excitatory and inhibitory transmissions leading to seizure activity (Pavlidou, 2007; Heida et al., 2009). More specifically, it is suggested that fever increases brain temperature, which in turn alters neuronal functioning through temperature-sensitive ion-channels and inflammatory processes promoting the secretion of cytokins, which together increase neuronal excitability and increase the probability of generating seizures (Leung & Robson, 2007; Pavlidou, et al., 2013; Reid, et al., 2009; Dubé et al., 2005; 2009). Overarching are on-going "chicken or the egg" debates arguing that either FS, particularly in cases of prolonged complex FS, may lead to hypoxic damage of the CNS and subsequently cause increased vulnerability to seizure activity, or fever

may trigger a seizure in pre-existing CNS disorders (Chang, et al., 2008). Taken together, FS have multifactorial and heterogeneous etiologies, leading to debates as to whether FS arise in otherwise healthy children, or as a result of an underlying although undetected predisposition, or whether this further depends on the type of FS suffered.

Risk Factors Associated this FS

Genetic Risk Factors

Population-based studies show that FS tend to occur more frequently in first-degree relatives of children with FS. In particular, 25% to 40% of affected children show a positive family history of FS (Chung, 2014). Moreover, the incidence is 20% to 25% higher among siblings and 10% higher among parents of children with FS (Hauser, et al., 1985; Knudsen, et al., 1996). Twin studies have similarly shown that predisposition to FS is higher among monozygotic twins (22%) than dizygotic twins (11%) (Waruiru, et al., 2004; Pavlidou, 2013).

No single susceptibility gene has been specifically detected for FS (Patel, et al., 2015), although several gene loci have been associated with the onset of FS. In particular, linkage studies have proposed 11 chromososmal locations responsible for FS, including FEB1 to FEB11 (Sghazadeh, 2014). Moreover, mutations in two voltage-gated sodium channel genes (SCN1A and SCN1B) and GABAa receptor gene have been identified in seizure disorders that often initially present as FS, including Dravet syndrome and GEFS+ (a syndrome in which individuals present with complex FS beyond the age of 5 and later develop afebrile seizures) (Kang, et al., 2006; Kira, et al., 2010; Abou-Khalil, 2010).

Environmental Risk Factors

The principle environmental factor involved in FS is the fever event, usually related to systemic infection. The most common causes for fever in FS are those associated with influenza A, gastroenteritis, otitis media, respiratory infection and human herpes simplex virus-6 (Millichap & Millichap, 2006, Kwong et al., 2006; Van Zeij, et al., 2004; Pavlidou, 2013). Other environmental factors related to poor outcome following FS include low family income and parental education (Leaffer, 2013). Developmental delay and neurological abnormalities prior to FS onset are further related to suboptimal outcome (Leaffer, 2013).

Risk of Initial FS

The risk factors associated with the development of an initial FS include a positive family history of FS in first degree relatives, a neonatal stay longer than 28 days, known developmental delay and day-care attendance (Chung, 2014). Children presenting with more than two risk factors have an increased chance of developing a first FS by 28%, and pre-existing developmental delay is most commonly associated with prolonged complex FS (Mastrangelo, et al., 2014).

Risk of FS recurrence

Following an initial FS, up to one third of affected children will have a recurrence (Patel, et al., 2015). Age at onset is the strongest and most consistent risk factor. When seizure onset occurs in the infantile period (younger than 18 months), the risk of recurrence is 50% (Cendes & Sankar, 2011; Pavlidou, 2013). Other risk factors for recurrence include a family history of FS in first-degree relatives, pathological prenatal history, low height and short duration of the

fever episode, focality and recurrence of seizures within the same febrile episode (Waruiru, et al., 2004; Pavlidou, et al., 2008). Children presenting with all these factors have up to an 80% chance of recurrence, whereas children presenting none of these factors have approximately a 4% chance of recurrence (Berg, et al., 1997; Patterson, 2013; Patel, 2015).

Risk of subsequent development of epilepsy

Approximately 2% to 6% of children suffering FS will subsequently develop epilepsy (Baumer, 2004; Abou-Khalil, 2007; 2010). The risk of developing an epileptic syndrome following simple FS is similar to that of the general population (1% to 2% risk), whereas the risk is increased following complex FS (4% to 7% risk) (Verity & Golding, 1991; Vestergaard, et al., 2007; Baumer, 2004; Abou-Khalil, 2010). Moreover, 35% of adults suffering from temporal lobe epilepsy (TLE), the most common focal epilepsy in adults, have a positive history of complex and/or prolonged FS in childhood (Reid, et al., 2009; Abou-Khalil, 2010). The main risk factors for later development of epilepsy include a positive family history of epilepsy, complex and/or prolonged FS and neurodevelopmental impairment (Abou-Khalil, 2010; Vestergaard, et al., 2007; Capovilla, et al., 2009). Causal links between these risk factors and the development of epilepsy are controversial and debated. It is argued that prolonged FS cause acute hippocampal damage resulting in residual hippocampal sclerosis, which represents the hallmark of TLE (Kira, et al., 2010). This hippocampal damage is argued to render the brain more vulnerable to seizures, which can eventually lead to epileptic syndromes (Barr et al., 1997; Harvey, et al., 1995; Wu, et al., 2005).

The impact of FS

Although research has shed significant light on the understanding of FS, despite certain links between FS and causes/consequences that remain unclear, outcome following FS is much less understood. Only relatively recently have FS been flagged as not being as benign as previously thought. Further investigations are required to bring better understanding to the impact of FS, given that they are the most common form of childhood seizure, particularly as they occur at a sensitive developmental age.

CEREBRAL DEVELOPMENT

From a structural perspective, neurons are developed and migrate to their final destination at approximately the 16th week of gestation, after which synapses and dendrites form connections, and axons begin to acquire myelin, which helps speed neural transmissions (Sidman & Rakic, 1973; Andersen, 2003). During the period immediately before birth, about 50% of all neurons are eliminated in a process of programmed cell death (i.e., apoptosis), a phenomenon which is believed to increase the efficiency of synaptic transmission (Andersen, 2003). Rapid cerebral development continues after birth, when the brain gains significant weight and volume. Processes involved in neuronal and network development begin to peak around the first year of life. Such processes include dendritic arborization and synaptogenesis, characterized by an explosion in the formation of neuronal connections, as well as myelination and synaptic pruning, characterized by the weeding of unnecessary connections and strengthening of utilized connections. The specialization of neurons and functions continue through infancy, childhood and into adolescence (Casaer, 1993, Andersen, 2003). The processes involved in cerebral development are argued to occur in a hierarchical manner, in

which neurons organize from the deepest layer to the outer-most layer and from posterior to anterior regions of the brain (Jernigan & Tallal, 1990; Andersen, et al., 2000). Moreover, the process of myelination is argued to similarly occur hierarchically from primary and sensory areas, to association areas and cortical regions, such that neurons involved in carrying sensory information are argued to be the first to acquire myelin, followed by neurons involved in carrying motor information, and so on in a hierarchical manner, until the myelination process reaches axons placed in the cortex (Casaer 1993; Hudspeth & Pribram, 1993; Staudt, et al., 1993). Even though anterior cortical regions are argued to be the last to reach maturity, evidence suggests that many areas of the cortex begin to function in infancy, including early specialization of the frontal cortex (Anderson, 2001). In particular, frontal behavior-related metabolic changes have been detected in infants as young as 6 months of age (Chugani, et al., 1987). EEG has been shown to change in relation to improved behavior during the first year of life (Bell & Fox, 1992), even though frontal regions show accelerated development from 7 to 10 years of age.

Understanding cerebral development through cellular and structural maturation can shed light on understanding how structure then relates to behavior and function and further, understanding of the mechanisms of how early life insults to the brain can impact cognitive development. Even though functional specialization occurs throughout childhood, into adolescence and even early adulthood, cognitive capacities begin specializing sufficiently enough at school-age (i.e., approximately 5 years of age) to allow for their specific evaluation through behavior (i.e., neuropsychological measures), in order to assess the impact of early life insults on particular cognitive capacities.

PLASTICITY VERSUS VULNERABILITY THEORIES

Although the extent and location of early life injury to the brain predict severity of residual impairment, timing of the injury will dictate the nature of the impairments. Following insults to the brain in early life, it was traditionally believed that owing to a lack of functional specialization, the young brain was "plastic" and able to adapt to injury, in that abilities subsumed by the damaged region could more readily reorganize and therefore recover function (Kennard, 1936). This is the assumption of Plasticity theory, which predicts that the earlier in life the insult occurs, the better the outcome in later life. This principle was established by early studies demonstrating normally developing intellectual and cognitive capacities in young children following focal brain injuries. In contrast, Vulnerability theory predicts that owing to the lack of functional specialization, the brain will attempt to recover endangered functions from a damaged structure by aberrantly creating faulty connections (Giza et al, 2002). Specifically, if damage occurs at a critical stage of development, cognitive skills already established will be spared, but those emerging and dependent on the damaged region may be irreversibly impaired. As such, a crowding effect will take place such that healthy neurons will take over damaged neurons in an attempt to recover the developing function. However, this phenomenon will limit these neurons' quantitative and qualitative resources, creating a "crowding" of cognitive functions for that particular tissue (Statz et al, 1994). Evidence from brain lesion studies has demonstrated that cognitive functions subserved by the cerebral structures that are under development at the time of the insult are the most affected (Anderson & Moore 1995; Dennis, 1989). In the evaluation of both theories, the

Vulnerability theory has been the most supported to date (Anderson, et al., 1997; Bittigau et al, 2004; Dennis, 1989).

With regards to seizure disorders in early life, it is argued that epileptogenic or abnormal electrical activity will compete with normal brain activity for neural resources (Pavlidou, 2007). If abnormal activity occurs at critical stage of cerebral development, aberrant neuronal connections may be formed and normal brain functions may fail to develop.

OUTCOME FOLLOWING FS

Physiological outcome

Animal Models

Animal models of experimentally induced FS, typically using a hyperthermia paradigm in rodents, consistently demonstrate altered hippocampal structure and function following FS. In particular, cytoskeletal changes have been demonstrated in hippocampal neurons within 24 hours following experimentally induced FS, for which altered functional properties of these neurons persisted into adulthood (Toth et al, 1998). Furthermore, MRI studies of experimentally induced FS show abnormally high T2 signal in the hippocampus, demonstrating marked anatomical abnormalities in the acute phase post-seizure, which were long-lasting (Dubé et al, 2004). Additionally, increased cytogenesis in the dentate gyrus and significant dark neuron formation following FS interpreted as marked neuronal injury has been observed, which further proved to be persistent effects of the FS (Nazem, 2012). In the predisposed rat brain, hippocampal damage characterized as atrophy associated with neuronal

loss has also been shown following a single episode of FS (Gibbs et al, 2011). Additionally, a decrease in dendritic spines in hippocampal neurons was found in these rats, which was associated with neuronal hyperexcitability. Indeed, long-lasting neuronal hyperexcitability has been consistently demonstrated in animal models following prolonged FS (Chen, et al., 1999; Brewster, 2002; Notenboom, 2010). This hyperexcitability following FS has been related to learning and memory impairments by a persistent decrease of the slow afterhyperpolarization (sAHP) in hippocampal neurons, characterized as a prolonged afterhyperpolarization that restrains repetitive firing underlying synaptic efficiency and therefore learning and memory (Kamal et al., 2006).

In Children

Loss of hippocampal integrity has also been demonstrated in children having suffered FSE. In the acute phase post-FSE, transient increases in hippocampal volume as well as signals of hippocampal hypertension as revealed by increased T2- weighted MRI relaxation times have consistently been demonstrated (Huang & Chang, 2009; Shinnar, 2003). Although some studies demonstrate resolution of acute abnormalities within the first few months following seizure onset, most argue for persistent residual sequelae (Shinnar, 2003).

Epidemiological studies of TLE have revealed that TLE patients with a prior history of FS demonstrate decreased bilateral hippocampal volume as compared to TLE patients without such prior history (Barr et al, 1997; Harvey et al, 1995). Furthermore, hippocampal sclerosis was found to be strongly associated with prior neurological insult in childhood, mostly characterized as prolonged FS (Harvey et al, 1995).

MRI volumetric analysis studies have similarly demonstrated loss of hippocampal integrity following FS. In particular, follow-up studies performed 4 to 16 months and further at 6 years post-FS have demonstrated that children having suffered from prolonged FS show hippocampal asymmetry, by evidence of a smaller right hippocampus (Scott et al, 2003; Merkenschlager et al, 2009). Furthermore, these asymmetries in hippocampal volume have been shown even when MRI scans done in the acute phase post-FS did not show abnormalities, indicating a progression toward hippocampal injury (Merkenschlager et al, 2009; Lewis, 2014). MRI volumetric analysis studies have also revealed hippocampal atrophy characterized as a decrease in hippocampal volume. In particular, longitudinal studies have demonstrated that most children having suffered prolonged FS showing acute hippocampal injury show hippocampal atrophy two-years after onset (VanLandingham et al, 1999; Provenzale, 2008; Hesdorffer, et al., 2008). Additionally, hypertense hippocampi as evidenced by increased T2-weighted MRI images at time of FS onset were correlated with hippocampal volume loss and even medial temporal sclerosis in some cases (Provenzale, 2008). Results of these longitudinal studies point to evolving hippocampal damage following complex FS, even in children who's initial scans showed no abnormalities.

It is important to note that most imaging research to date has been completed in children having suffered prolonged FS and FSE. The few studies that have investigated the impact of other complex features on cerebral development have revealed persistent MRI hippocampal abnormalities in both prolonged and focal FS (Hesdorffer, et al., 2008), whereas other studies

have demonstrated a greater impact of multiple seizures on hippocampal volume loss as compared to focality and duration of the seizure (Yoong, et al., 2013).

Moreover, the vast majority of imaging studies have focused on the development of the hippocampus. Although it is argued to be the most affected structure in FS and FSE, next to no research has been performed in investigating hippocampal abnormalities in the larger context of brain development, specifically how alterations in the hippocampus might impact the development of other structures, or inversely, how alterations in other structures might impact hippocampal development. Indeed, the hippocampus is a structure that plays an active role in larger networks, the cortico-hippocampal network in particular. The function of this network is known to play an integral part in learning and memory (not just as a function of the hippocampus in isolation). Moreover, given the direct and monosynpatic connections between the hippocampus and frontal/prefrontal areas, including the medial prefrontal cortex known for its involvement in executive functioning, a set of cognitive processes involved in the cognitive control of behavior (e.g., inhibition, self-monitoring, goal-directed behavior), it is possible that damaged hippocampi following FS may result in cognitive challenges beyond learning and memory.

Cognitive outcome following FS

Animal models

Animal models of experimental FS in rodents have shed light on cognitive difficulties following FS. Notably, it has been found that hyperthermia-induced FS in predisposed rat brains resulted in impairments on the Morris Water Maze task, a task of learning and memory

(Scantleburry, 2005; Rajab 2014). Furthermore, cognitive testing of adult rats that suffered hyperthermia-induced FS as pups without early cortical lesion demonstrated deficits in working and reference memory in the Morris Water Maze task (Dubé et al., 2009; Rajab 2014). Additionally, these deficits were shown to be related to impaired hippocampal function and structure (i.e., as shown by an abnormally high T2 signal). Taken together these animal models of early life FS demonstrated learning and memory impairments in adult life following an experimental FS event. The FS induced in these animals are considered to be at the "severe" end of the spectrum of FS, and would correspond to FSE in humans (Roper, 2016). Moreover, animal models have focused on spatial learning, as it is challenging to test other types of learning in rodents, and have overall focused on abilities largely dependent on hippocampal functioning. Although these studies provide valuable insight into the deficits observed in the most severe form of FS, they lack evidence related to other possible deficits following different types of FS.

In children

The impact of complex FS on cognitive development and behavior in children remains unclear. Although converging evidence suggests unaltered global intelligence following complex FS and FSE, the impact of these types of seizures on specific cognitive functions, beyond intelligence, is debated. While some studies indicate unaltered development, scholastic achievement and behavior following complex FS, others argue for hindered developmental trajectories and disrupted behavior following the event (Ellenberg & Nelson, 1978; Verity et al., 1998; Hirtz, 2002; Martinos, 2012; 2013; Weiss, 2016). Divergent evidence has typically been the result of inconsistent methodologies and populations studied. Early studies denying

any impact of FS on cognitive development used measures that lacked specificity and objectivity (i.e., surveys). Using more specific, objective and standardized measures, other studies have revealed contrasting evidence regarding the impact of complex FS on cognition and behavior in school-age children, although discrepancies in methodologies are further noted, including populations used (i.e., population versus hospital-based samples), complex seizure type studied (i.e., prolonged versus multiple versus focal), measures used (i.e., objective versus subjective) and time points assessed (i.e., varying time points since seizure onset or last seizure occurrence) (Kolfen et al., 1998; Chang et al., 2000; 2001; Norgaard et al., 2009; Visser et al., 2012).

Understanding early developmental outcome, within the first year-post FS onset, could shed light on the understanding of long-term cognitive outcomes. Few studies to date have investigated development within the first year-post seizure onset. In particular, children having suffered FSE have been shown to develop normally within the first month post-seizure onset, although demonstrated slightly weaker motor development and receptive language one year-post onset (Weiss, 2016). Children having suffered a prolonged complex FS consistently demonstrated worse developmental outcome as compared to controls 6 weeks and 1 year following seizure onset (Martinos, 2013), as well as accelerated forgetting within the first month and 1 year following onset (Martinos, 2012). Weaker development one year-post onset has further been linked to hippocampal anomalies in children having suffered prolonged seizures (Weiss, 2016; Martinos, 2012). These results suggest a possible worsening of the impact of the initial seizure on development over time, particularly in the context of neurodevelopment, as FS occur during a period of rapid cerebral development and functional

specialization (Andersen, 2003). However, studies to date have focused on FSE, forgoing the investigation of the possible impact of focal and recurrent seizures on development, even though they have also been shown to alter structure (Hesdorffer, et al., 2008; Yoong, et al., 2013). Moreover, the impact of seizure duration on cognition can be considered somewhat biased in the FSE studies, as their mean seizure duration varied between 70 and 90 minutes (Weiss, 2016; Martinos, 2012). It is still unknown whether a less prolonged FS, that is, lasting between 15 and 20 minutes, may have a similar or commensurable impact on cognition.

Beyond the impact of complex FS on development, studies investigating their impact on cognition have focused on hippocampus-dependent functions, mainly learning and memory. In particular, infants having suffered FSE have demonstrated reduced memory capacities, as well as accelerated forgetting within the first year post-onset, which were associated with reduced hippocampal volume (Weiss et al., 2016; Martinos et al., 2012). Other studies investigating school-age children having suffered non-prolonged complex FS found that although memory performances were similar between FS and control groups, mechanisms used to achieve similar behaviors were different, evidenced by altered event-related potentials and hemodynamic activity (Kipp et al., 2010; 2012).

With regards to their impact on behavior, complex FS have been associated with increased external behavioral deficits and increased attentional difficulties as measured by parental questionnaires (Kolfen et al., 1998; Lippé et al., 2009; Tsai et al., 2015). More objectively, very few studies to date have examined the impact of complex FS on executive functioning later in life. Roy et al (2011) demonstrated that children of 2 years of age showed reduced self-

monitoring and inhibition abilities following a single episode of SE. They compared these children to two control groups, namely children having suffered a FS and otherwise healthy controls. Their results indicated that although children having suffered from an episode of SE performed worse than healthy controls, children having suffered FS did not differ significantly from either SE or control group, suggesting that an episode of FS may hinder these functions, albeit to a lesser extent. In investigating FS per se, children having suffered complex FS have been shown to demonstrate weaker sustained attention abilities (Hara et al., 1986), although other studies have suggested better performances in children having suffered FS (Chang et al., 2000; 2001). The results of the latter two studies however reveal that although children having suffered complex FS were better at sustaining their attention on complex tasks, they had more difficulty sustaining their attention on simple tasks as compared to controls, which could possibly indicate a need for arousal and challenges in self-monitoring abilities. To our knowledge, no study has yet objectively and specifically assessed executive functioning in children having suffered complex FS beyond working memory and sustained attention abilities.

Overall, studies investigating the impact of complex FS on cognition have to date mainly focused on FSE and hippocampus-dependent functions. Exploring the effects of other complex features (i.e., recurrence and focality) on these functions, as well as on others that could be affected by faulty hippocampal function through cortico-hippocampal networks, including executive functions, could help increase our understanding of the impact of FS on cognition. Moreover, investigating their impact on cognition as a factor of time (i.e., age), could help

understand the evolution of possible challenges through early development, a time when significant maturational changes and functional specializations occur in the brain.

RESEARCH OBJECTIVES AND HYPOTHESES

1. The first objective was to review cognitive sequelae following Status Epilepticus, the most severe form of a seizure in childhood, through a more extensive review of the literature than previously available.

2. The second objective was to investigate development and cognition from onset to school-age following complex FS, as compared to children having suffered simple FS, in the context of known risk factors for poor outcome, including all types of complex features. More specifically, we aimed to transversally evaluate development within the first year-post seizure onset, as well as cognition in a cohort of children old enough for cognitive functions to be sufficiently differentiated (i.e., school-age).

   It was hypothesized that infants having suffered complex FS would show hindered development as compared to simple FS controls, within the first year-post onset. It was further hypothesized that school-age children having suffered complex FS would show weaker performances on measures of learning/memory and executive functioning as compared to simple FS controls, given the role of the hippocampus in FS, and the possible impact of this early life insult on the development of

structures subserving executive functions, which are crucial for academic success. Lastly, it was hypothesized that developmental and cognitive measures would be associated with known risk factors for poor outcome, including younger ages at onset and longer seizure durations.

ARTICLE 1

COGNITIVE OUTCOME OF STATUS EPILEPTICUS IN CHILDREN

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ABSTRACT

Epileptic encephalopathy encompasses conditions in which cognitive, motor or sensory deficits result as a consequence of epileptic activity defining certain syndromes. It therefore represents a more severe subset of epilepsy, which can be generally characterized as frequent or severe seizures leading to cerebral dysfunction. This disturbance in cerebral functioning can in turn hinder, somewhat dramatically, cognitive development and further impact the future lives of patients. In this review, we describe the cognitive consequences of Status Epilepticus in children and in adults in the context of plasticity theories. Recent studies maintain that consequences of SE may be severe cognitive sequelae, especially in early life. Since the residual consequences of SE in adulthood seem less detrimental and long-lasting, we argue that early life insults, such as those created by SE, during a rapid period of development and functional specialization, result in specific cognitive deficits dependent on the sensitive period at which SE occurred.

1. INTRODUCTION

Epileptic encephalopathy encompasses conditions in which cognitive, motor or sensory deficits result as a consequence of epileptic activity defining certain syndromes (1). It therefore represents a more severe subset of epilepsy, which can be generally characterized as frequent or severe seizures leading to cerebral dysfunction. This disturbance in cerebral functioning can in turn hinder, somewhat dramatically, cognitive development and further

impact the future lives of patients. In this review, we consider Status Epilepticus as an epileptic encephalopathy owing to its impact on cognitive development in early life.

2. STATUS EPILEPTICUS (SE)

Status Epilepticus (SE) is a medical epileptic emergency characterized by either rapidly repeating seizures without recovery or regain of consciousness between episodes, or prolonged continuous epileptic activity, both creating a fixed or lasting condition (2, 3). It is an event rather than a syndrome. It is accepted that the duration of an episode of SE is 30 minutes or more, period after which cerebral functioning is highly probable of being affected and immediate medical attention is needed (4). Recently, the notions of impending SE and established SE have been introduced (5) in order to provide the best possible care for patients presenting with SE. In adults, patients presenting a seizure lasting more than five minutes can be designated as impending SE. In children, impending seizures are considered when seizures last between 5 and 10 minutes (5).

The prevalence of SE varies. Three epidemiologic studies suggest 17 to 108/100000 as being the prevalence of SE (6, 7, 8). Although SE can occur at any age, it is most often encountered in infancy and childhood, 40% of all cases occurring prior to 2 years of age, a period in which the brain is in rapid development (9). Such prevalence is argued to be present in early life owing to the exceeding amount of neurons and excitatory connections prior to functional specialization while undergoing neuronal pruning, which increases the vulnerability of the developing brain to SE (10). In affected children, an imbalance between inhibitory and

excitatory neurotransmissions is argued to lead to anomalies in neuronal impulses leading to prolonged seizures (11). In fact, the pathophysiology of SE seems to involve a loss of inhibitory mechanisms, which result in a deficiency of the neuronal metabolism, which is unable to keep up with the demands of the continuous epileptic activity (12). The seizures are most frequently generalized, but may also be partial and either convulsive or non- convulsive (13). SE is further classified in accordance with its respective etiology (14). Idiopathic SE occurs in otherwise healthy individuals without metabolic dysfunction nor an acute insult to the Central Nervous System (CNS). Furthermore, remote symptomatic SE occurs in patients with a history of insult to the CNS without acute provocation such as in mental retardation. Febrile SE, the most common etiology in children (15), occurs when the only provocation of the CNS is a high fever, usually higher than 38,4 degrees Celsius. In this population, 86% of children demonstrate normal prior development (16). Acute symptomatic SE occurs during an acute illness with a known insult to the CNS such as in meningitis. Although there has been debate on the long-term effects of SE on cerebral functioning, recent research investigating more accurately the cognitive sequelae related to SE demonstrate that cognitive functions under development are exposed to being altered and damaged in children presenting with SE, owing to its high incidence in infancy, a period of marked and rapid cognitive development.

3. PLASTICITY VS. VULNERABILITY IN THE DEVELOPING BRAIN

In considering the impact of an early insult on cerebral and cognitive development, two opposing theories are contradictory in their predictions. The Plasticity theory posits that the young brain is flexible and therefore capable of recovery after insult. As such, since there is

less functional specialization in early life, functions that would depend on a damaged area would simply reorganize to functionally cope with the insult (17, 18). As such, this theory predicts that early brain damage is the most biologically manageable, resulting in less vulnerability to the impact of damage as opposed to an older brain. In contrast, the Vulnerability theory posits that the young brain is the most fragile and therefore vulnerable to early insult. It argues that owing to the lack of functional specialization, the brain will attempt to recover endangered functions, but will do so aberrantly creating faulty connections in early life (19). As such, a crowding effect will take place such that healthy tissue will take over the damaged tissue in attempting to recover the cognitive function at hand, but consequently limiting the tissue's quantitative and qualitative resources (20). This effect was first demonstrated in the context of hemispheric dominance following left hemisphere damage in early life such that an insult to the left hemisphere prior to one year of age resulted in the proper development of language but faulty development of non-verbal skills; owing to brain plasticity, the emerging language functions took over neurons dedicated to non-verbal skills. The reverse effect was observed when the insult occurred after one year of age (20, 21). As such, healthy tissue, although already specialized for a certain function will forgo that specialization for the proper development of the function underlying the insult, creating a "crowding" of cognitive functions for that particular tissue Therefore, the Vulnerability perspective of the developing brain predicts that early life insults are the most difficult to recover from.

In further investigating the opposing predictions of both theories of the impact of early insult on the developing brain, the Vulnerability theory has been the most supported (22, 23, 24, 25).

It has been found that young neurons more readily grow to make new connections, which following an insult, may facilitate aberrant connections (26). As such, the developing brain is the most vulnerable to insult resulting in subsequent damage post-SE potentially persisting in later life. Furthermore, findings demonstrate that not only is the severity of the sequelae following SE predicted by the extent and location of the insult, but the nature of the sequelae itself is determined by the timing of the SE episode (27). As such, the developmental period at which the insult occurs is argued to predict which cognitive functions will be most affected and therefore predict the general outcome of the patient.

4. A MODEL OF HUMAN DEVELOPMENT

In concordance with the Vulnerability theory, early insults to the brain have the most detrimental impact on cerebral and cognitive development persisting in later life. As such, faulty neuronal connections following an early life insult during a critical period of development will hinder the normal development of brain functions, for which the sequelae will persist in later life (28). However, already developed functions at the time of the insult will be spared. The notion of critical periods during infancy through adolescence is widespread and generally accepted (29). Critical periods allow for a logical hierarchy in development such that windows of opportunity allow for the specialization of functions. Furthermore, certain structures and their underlying function must be well specialized prior to others. As such, sensing pathways such as those involved in vision and hearing must develop prior to language pathways, which in turn must develop prior to higher cognitive functioning, including executive functions (29). Critical periods, consequently, expose certain functions as

more vulnerable than others at particular and specific periods during development. The vulnerability of different cognitive functions therefore varies with the developmental process itself. In the presence of an early insult to the brain, the function under development will be hindered, affecting not only that particular function, but also the development of subsequent functions dependent on the hindered one. Healthy development of cognitive functions depends on the integrity of the structure the function underlies. As such, following an early life insult, the integrity of a particular structure is compromised, further compromising the cognitive function that structure is responsible for.

5. PHYSIOLOGICAL ALTERATIONS RESULTING FROM SE

Prolonged and frequent seizures, such as those involved in SE consistently show physiological brain damage. In fact, the physiological properties of cells have been shown to be altered following an SE event (30, 31). The most vulnerable structure to the seizures is the hippocampus, which is involved in learning and memory. Hippocampal edema, cell loss particularly in the Sommer sector, and abnormalities have consistently been detected within this structure following SE (32, 10). Also in human, other structures have been demonstrated to show necrosis following events of epileptic attacks such as the amygdala, dorsomedial thalamic nucleus, medial layers of the neocortex, cerebellum, the piriforme and entorhinal cortices (32, 33, 30, 31). Neuronal degeneration and loss in these areas have been shown to occur rapidly after a SE event (34, 30). Cerebral atrophy has also been demonstrated following SE (35). Animal studies have further supported these physiological alterations. The work of Meldrum involving induced SE in baboons has demonstrated similar neuronal necrosis

involving the neocortex, hippocampus, amygdala, thalamus and cerebellum (36). In a long-term follow-up, different SE animal models have found structural changes (37, 38, 39). For example, smaller volumes of the hippocampus, thalamus, putamen and perirhinal cortex have been found (39). Interestingly, severity of hippocampal volume loss correlated with severity in spatial learning impairments. Of note, animal data describing the consequences of an induced single episode of SE tend to show greater deleterious consequences in immature rat brains in comparison to adult rat brains (40). Although physiological alterations following SE have been shown specifically and consistently, the cognitive sequelae resulting from these abnormalities is not as clear and widespread.

6. COGNITIVE SEQUELAE OF STATUS EPILEPTICUS IN ANIMAL MODELS

Cognitive sequelae following SE were first studied using animal models in which animals showed a normal development until seizure onset. Following induced SE in rat pups, impairment in emotional behavior was observed, characterized by an increase in anxiety and fear (41, 42). Furthermore, increased hyperactivity and spontaneous exploratory behavior was shown with a similar experimental design (41, 43). Also, owing to the vulnerability of certain structures involved in the limbic system such as the hippocampus and amygdala, learning and memory impairments are consistently marked. Learning deficits, usually demonstrated by decreased habituation and reduced adaptations to novelty, are observed following SE, and these deficits persist into later life in rodents (41, 42, 44). Also owing to acquired anomalies in these limbic structures, spatial and emotional learning and memory are impaired shortly after SE (45, 42, 43). Memory impairments were thus marked in these models (45). Whether these

findings can generalize to the impact of early SE on the development of these cognitive functions to humans is a matter of debate. However, recent research has argued for cognitive sequelae resulting from SE in early life.

7. COGNITIVE SEQUELAE OF STATUS EPILEPTICUS IN HUMANS

7.1 Children

Cognitive sequelae resulting from SE in early life have been demonstrated. In general, studies demonstrate progressive structural and functional alterations following SE, generally reporting broad cognitive consequences of SE. Even so, deficits in verbal and non-verbal intellectual ability have been identified following SE (47, 48, 49). Furthermore, global IQ deficits are demonstrated in early onset seizures (48, 26). Several landmark studies have well demonstrated the presence of cognitive deficits following SE in early life. Aicardi & Chevrie (50) retrospectively studied 239 children having undergone one episode of SE lasting one hour or more, under the age of 15. Fifty seven percent (57%) of the cohort presented with mental or neurological sequelae. More specifically, 20% of the cohort developed motor delays and 33% presented IQs lower than 80, all in children whose development was unremarkable prior to the SE event. Furthermore, 48% presented with mental retardation following the episode, the majority of affected children again demonstrating normal development prior to SE. Furthermore, Yager (51) followed 52 children over 18 months following an episode of SE. Twenty eight percent (28%) of otherwise healthy children developed neurological sequelae following SE, and 25% of children who were predisposed to pathologies including previous epileptic activity deteriorated further following SE. Lacroix (52) also longitudinally followed

147 children following an episode of SE. Thirty percent (30%) showed a neurological deficit following SE at discharge, and 68% of these children still demonstrated these deficits one year after. Taken together, these data demonstrate marked cognitive and neurological dysfunction following SE, supporting the Vulnerability theory of insult to the developing brain. However, even though dysfunctions are shown, the specific nature of the deficit remains unclear. The lack of appropriate and specific methods in evaluating the deficits makes conclusions general and non-specific. Neuropsychological testing is however a good tool in evaluating the specific cognitive functions potentially affected as opposed to the assessment of level of functioning as a whole. Neuropsychological testing is advantageous since it can easily be adaptable to the hospital setting, however it should be noted that in infants, the age at testing poses a certain constraint on the sophistication of the assessment.

In taking these limitations into consideration, a recent study by Roy et al (53) further assessed the Vulnerability theory by studying the effect of a single episode of febrile SE on the developing brain in otherwise healthy children. They specifically examined psychomotor function as well as executive functions in these children. Executive functions, mainly involved in regulation of behavior, begin rapid development in early life, continuing through to adolescence (54, 55, 56) and are the underlying functions of the frontal lobes. Since executive skills are developed in different trajectories over a longer timeframe during development, comparing the impact of an insult at different times during this development can shed light onto its potential differing consequences. Following the hierarchy in the development of the brain, the frontal lobes depend on the structural and functional integrity of other structures as they encompass higher cognitive functions. An early insult to the brain would therefore hinder

executive functions. Roy et al (53) compared younger and older children in differing critical periods using neuropsychological testing to evaluate the prediction that the function under development would be the most vulnerable to an insult. This is precisely what they found. In younger children (prior to 11 months of age) presenting with a febrile SE, hand-eye coordination and motor ability were most affected but were spared in older children. In contrast, older children presenting a febrile SE demonstrated personal and social deficits. Similarly, Anderson et al (26) had previously demonstrated, with a larger age range of children and of insults, that consequence of early brain insult on executive functions was dependent on which critical period the episode occurred. As such, an insult prior to 2 years of age demonstrated deficits in goal-setting, a skill spared in children whose onset was in middle or late childhood. Furthermore, an insult prior to 3 years of age was associated with deficits in cognitive flexibility and working memory, these skills being spared in those for which SE episode occurred after the age of 10. It is important to note however that Anderson et al (26) did not investigate the impact of an episode of SE per se, but rather the impact of early brain insult in general and as such, did not take the underlying etiologies into consideration. Indeed, studies in school age children presenting with SE are lacking. Roy et al (53) however, investigated children affected precisely by Febrile SE and not only used healthy matched controls, but also included a control group composed of children affected by a simple Febrile Seizure (FS). Simple FS are brief (less than 15 minutes) and are argued to be unremarkable in their effects on the developing brain. As such, prolonged (SE) seizures were compared to brief (FS) seizures allowing to isolate the impact of fever and brief seizures themselves. Taken together, this particular study alone gives important insight into the presence and specific

cognitive impairments observed following a single febrile SE episode in otherwise healthy children.

7.2 Adults

Patterns of cognitive sequelae following SE in adulthood seem to differ than those seen in infancy and childhood. In a prospective study of SE occurring in adults (mean age was 40) with no underlying pathology, Adachi et al (57) did not demonstrate intellectual deficits following the episode as evaluated by neuropsychological testing (WAIS-R), but rather both the experimental and control group of matched healthy individuals could not be differentiated. This finding was also previously demonstrated (58). In fact, resolution of long-lasting SE cognitive sequelae in adults have been demonstrated 6 to 24 months post-SE episode, and resolution of acute sequelae have been shown to resolve within 1 to 4 weeks, suggesting a reversible effect of the residual consequences of SE. Also demonstrating this effect was a case report of a 25 year-old women with a history of epilepsy starting at age 14, hospitalized after a SE episode (59). Neuropsychological testing demonstrated severe memory and executive function deficits at the time of the insult. However, one year after the insult and following unremarkable antiepileptic treatment, the cognitive deficits were reversed and the women returned to her Master's studies. These data of the impact of SE in adulthood suggest that it's effects are less severe than in childhood, such that not only do studies show unremarkable intellectual deficits following SE, but also show reversible effects of the deficits. It should be noted however that the SE described above were idiopathic. Symptomatic epilepsies in contrast involve greater presence and severity of cognitive impairments. However, even though the case study presented was symptomatic and still demonstrated reversible effects,

etiology, and potentially other aspects underlying the SE episode, must be taken into account when considering its impact on cognition.

8. OTHER ASPECTS POTENTIALLY UNDERLYING COGNITIVE DECLINE IN SE

Whether an episode of SE results in cognitive deficits seems to not only rely on the onset of SE (infant vs. adult) but rather on a web of interweaving aspects related to epilepsy and SE. Certain risk factors have been shown to affect prognosis following such an episode.

8.1. Etiology

The origin of the SE is an important risk factor. As there are several possible etiologies, the cause of SE can interplay with the actual seizures with regards to outcome. Idiopathic SE tends to have a more favorable prognosis than symptomatic SE (48, 51, 60). Furthermore, a typical pattern of development prior to the episode is related to better outcome (52). In contrast, the risk of developing epilepsy increases to more than 50% in convulsive symptomatic SE. In addition, more than 20% of children with acute symptomatic SE show new cognitive impairments compared to less than 10% in other types of SE (61). The risk for SE is increased in neurologically deficient children (50) and children with a history of seizures are at higher risk for neurological sequelae (62). Additionally, younger children tend to have more severe etiologies, as a decrease of acute symptomatic cases is observed after the first year of life (9). However, 75% of children under 2 years of age demonstrated normal development until the insult (9). In general, the presence of an organic etiology is related to poorer prognosis (48). It should be noted however, that cognitive effects of the seizure itself

without an underlying pathology have been reported (63, 64). Taking etiology into account, if not cautious with the methodology used, the cause of the potential observed deficiency (etiology vs. SE) can be confounded (4).

8.2. Duration and Frequency of Seizures

Longer durations of a SE episode are related to increased risk for deficits (65, 60). In fact, it has been demonstrated that episodes lasting less than one hour result in neuronal injury, and episodes lasting more than one hour result in neuronal death (66), supporting the previous argument. Duration of SE is also related to etiology such that prolonged episodes typically accompany more severe etiologies (67).

Recurrent seizures are more persistent in individuals with prior neurological abnormalities (68). Controversies exist as to the impact of recurrent seizures on cognition. It has been proposed that recurrent seizures lead to cognitive impairment, specifically, intellectual and memory deficits (68, 45). Also, it has been shown that a long history of seizures is associated with mental deficits (69). Furthermore, it has been demonstrated that early life seizures result in long-term deficits (70), further supported by an animal model demonstrating deficits in learning and memory following recurrent SE (70). In contrast, it has also been proposed that recurrence of seizures itself does not pose a risk for cognitive development (68,71). As demonstrated in SE, some epileptic models do not always demonstrate aggravated consequences of recurrence of seizures (72). Following this perspective, in epileptic patients, it is suggested that the predisposed brain develops somewhat of a tolerance to the impact of

seizures therefore producing less damage, whereas the naive brain is more vulnerable to one insult (74). This perspective is however very delicate and must be debated.

8.3. Age at onset

The risk involved in the age at onset of SE has been covered in this review such that, thus far it has been shown that SE onset in early life, a period at which individuals are more prone to SE, has a greater impact on cognitive functioning than in later life, in which even reversible effects are observed. As discussed under the related effects of etiology, SE presents greater severity in children as they more often show a symptomatic etiology than in adults (9, 50). Furthermore, adults presenting with SE tend to have a history of seizures (9). As such, consideration must be taken of the underlying etiology in the younger SE population on interference with development. In adults however, age at onset and duration of the SE episode has not been related to prognosis (55).

8.4. SE as cause of injury

In animal models, brain injuries following SE have been repetitively revealed. In children, SE can cause hippocampal lesions, at least in the acute phase (34). Further studies are needed to investigate if long-term hippocampal MRI volume loss are due to reduced edema or to a loss of neuronal tissue. Furthermore, more human studies are needed to establish the link between hippocampal lesions following SE and cognitive impairments. This could be facilitated with the recommended use of MRI in cases of SE (75). Investigating the link between these lesions in the limbic system and behavioral impairments could also be interesting and perhaps shed even more light on patient outcome following SE.

8.5. Other

With respect to gender, males have a higher propensity of developing symptomatic SE in contrast to females, which demonstrate a higher propensity of developing idiopathic SE (50). However, gender itself does not have an impact on prognosis following a SE episode. It has also been suggested that an enriched environment can aid in memory decline such that enriched environments facilitate hippocampal plasticity, which in turn leads to bettered formation of Long-Term Potentiation (76). In contrast, race does not influence this prognosis (77, 49).

Taken together, several marked risk factors must be taken into consideration in evaluating the impact of SE on cognition such that several confounding variables are possible. However, awareness and caution in the methodologies and analyses used can shield from the confounding effect of these risk factors.

9. IMPACT OF ANTIEPILEPTIC TREATMENT (AED) ON COGNITION

Antiepileptic drugs (AED) have various effects between patients as well as between seizures and epilepsy types. The success of AED is usually measured as a reduction in the number of seizures, not necessarily as its impact on cognition following epilepsy (78). As such, evaluation of cognitive ability following treatment poses more difficulty. In fact, some AED themselves have been shown to induce cognitive deficits such as mild memory, attention and psychomotor problems (79). Even though no comparative studies have been performed to

investigate the side effects of more recent AED, it has been argued that Topiramate is involved in attention, concentration and memory problems (80). Taken together however, it is suggested that use of AED is not the major factor causing cognitive comorbidity in epileptic encephalopathies (81). In SE, it has been demonstrated that cognitive outcome following SE depends on the time between the episode and the initiation of treatment (50, 60). AED administered during an SE episode, in contrast to those administered in most epileptic conditions, are usually termed "aggressive treatment" since they are meant to be administered very rapidly and withdrawn within the following 24 hours (82). Its purpose is to shorten the episode in hopes to protect against neuronal damage and therefore to potentially protect against the cognitive sequelae related to prolonged episodes (60, 82). As such, AED have been shown to reduce cognitive sequelae following an episode (50, 60). This was also observed in animal models (83). More specifically, the use of AED in children presenting with SE has demonstrated a control of the seizures that resulted in a prevention of further cognitive deterioration (82). Although AED stopped further cognitive sequelae, they did not allow recovering maladapted functions. Since AED did not allow recovering of anomalies in cognitive functions since SE onset, our argument that an insult to the developing brain at particular sensitive periods is detrimental to cognitive development is further supported.

10. CONTROVERSIES

Even though we are arguing that SE has an unforgiving impact on cognitive development, as in any body of literature, results can be controversial. Firstly, a poor prognosis in early life SE has not always been reported (67, 84). Also, it has been reported that the underlying causal

factor of SE is related to outcome as opposed to age at onset (61, 85). However, there are certain methodological considerations in these and other studies. Lack of standard categorization of underlying etiologies, as well as lack of consideration for type and frequency of seizures between testing could impact results. Furthermore, heterogeneous groups are often compared relative to age at onset, duration and frequency of seizures, etiology, treatment as well as genetic factors also creating potential confounds (73). Furthermore, it has been observed that retrospective studies tend to show greater intellectual deficit following SE than prospective studies (57). In addition, measures of cognitive ability are often lacking accuracy and specificity such that deficits in specific skills are overlooked when simply assessing global IQ. IQ itself is not an appropriate measure for cognitive dysfunction. As such, more specific tests should be used in attempt to measure the cognitive skills of interest, such as would allow neuropsychological assessments. Again, this type of assessment is advantageous such that tests can be selectively chosen for each patient or each group of patients, categorized by site of lesion for example, in order to better comprehend the precise pervading deficits as opposed to a simple level of intelligence.

11. DISCUSSION

In spite of these controversies and methodological issues, we maintain that consequences of SE may be severe cognitive sequelae, especially in early life. More recent studies more readily take these methodological issues into account creating a better experimental design. Also, they use more specific tests and aim and specific cognitive functions. As such, these recent results better demonstrate the presence and severity of the cognitive sequelae resulting from SE in

infancy. Since the residual consequences of SE in adulthood seem less detrimental and long-lasting, we argue that early life insults, such as those created by SE, during a rapid period of development and functional specialization, result in specific cognitive deficits dependent of the sensitive period at which occurred SE. These deficits can potentially lead to deficits in later childhood expressed as such as learning disabilities, the residua of which may persist into later life. Further investigations involving the long-term effects and impacts of early life SE on later development and later life functioning are needed. Although adult-onset SE seems to spare the cognitive integrity of affected patients, it is still unknown whether early-onset SE has detrimental impacts in later life.

REFERENCES

(1) Dulac, O. Epileptic Encephalopathy. *Epilepsia* 1992; 42, 23-26.

(2) Gestaut, H. *Dictionary of epilepsy*. Part I. Definition. Geneva: World Health Organization, 1973.

(3) Gestaut, H. A new type of epilepy: benign partial epilepsy of childhood with occipital spike-waves. *Clin Electroencephalogr* 1982; 13, 13-22.

(4) Hauser WA. Status epilepticus, frquency, etiology, and neurological sequelae. In: Deglado-Escueta, A, Waterslain, C, Treiman, D, et al. *Status Epilepticus*. New York: Raven Press, 1983: 3-14.

(5) Freilich, E., Jones, J., Gaillard, W, et al. Novel SNC1A mutation in a proband with a malignant migrating partial seizures of infancy. *Arch Neurol* 2011; 65-5, 665-671.

(6) Chin, R., Neville, B., Peckham, C., Wade, A., Bedford, H., Scott, R. Treatment of community-onset, childhood convulsive status epilepticus: a prospective, population-based study. *The Lancet Neurology* 2008; 7-8, 696-703.

(7) Sadarangani, M., Seaton, C., Scott, A., et al., Ogutu, B., Edwards, T, Prins, A., Gatakaa, H., Idro, R., Berkley, J., Peshu, N., Neville, B., Newton, C. Incidence and outcome of convulsive status epilepticus in Kenyan children: a cohort study. *The Lancet Neurology* 2008; 7-2, 145-150.

(8) Nishiyama, I., Ohtsuka, Y., Tsuda, T., Inoue, H., Kunitomi, T., Shiraga, H, Kimura, T., Fujimoto, K. An epidemiological study of children with status epilepticus in Okayama, Japan. *Epilepsia* 2007; 48-6, 1133-1137.

(9) Shinnar, S., Pellock, J., Moshé, S, Maytal, J., O'Dell, C., Driscoll, S., Alemany, M., Newstein, D., DeLorenzo, R. In whom does status epilepticus occur: age-related differences in children. *Epilepsia* 1997; 38-8, 907-914.

(10) Wasterlain, C., Fujikawa, D., Penix, L., Sankar, R. Pathophysiological mechanisms of brain damage from status epilepticus. *Epilepsia* 1993; 34-1, S37-S53.

(11) Scott, R., Surtees, R., Neville, B. Status epilepticus: pathophysiology, epidemioloogy, and outcomes. Arch Dis Child 1998; 79, 73-77.

(12) Pellock, J. Status epilepticus un children: update and review. *J Child Neurol* 1994; 9, 2S27-2S35.

(13) Lowenstain, D., Alldredge, B, Pharm, D. Status epilepticus. *The New England Journal of Medicine* 1998; 338-14, 970-976.

(14) Maytal, J., Shinnar, S., Moshé, S., Alvarez, L. Low morbidity of status epilepticus in children. *Pediatrics* 1989; 83-3, 323-331.

(15) Fountain, N. Satus epilepticus: Risk factors and complications. *Epilepsia* 2000; 41-2, S23-S30.

(16) Shinnar, S., Hesdorffer, D., Nordli, D, Pellock, J., O'Dell, C., Lewis, D., Frank, L., Moshé, S., Epstein, L. Marmarou, A., Bagiella, E. Phenomenology of prolonged febrile seizures; results of the FEBSTAT study. *Neurology* 2008; 71-3, 170-176.

(17) Kennar, M. Age and other factor in motor recovery from precentral lesions in monkeys. *American Journal of Physiology* 1936; 115, 138-146.

(18) Woods, B. The restricted effects of right-hemisphere lesions after age one: Wechsler test data. *Neuropsychologia* 1980; 18, 65-70.

(19) Giza, C., Prins, M., Hovda, D. Herschman, H. Feldman, J. Genes preferentially induced by depolarization after concussive brain injury: effects of age and injury severity. *Journal of Neurotrauma* 2002; 19-4, 387-402.

(20) Statz, P., Strauss, E., Hunter, M., Juhn, W. Re-examination of the crowding hypothesis: Effects of age at onset. *Neuropsychology*, 1994; 8-2, 255-262.

(21) Lansdell, H. Verbal and non-verbal factors in right-hemisphere speech: Relation to early neurological history. *Journal of Physiological and Comparative Psychology* 1969; 69, 734-738.

(22) Anderson, V. & Moore, C. Age at injury as a predictor of outcome following pediatric head injury. *Child Neuropsychology* 1995;1, 187-202.

(23) Anderson, V., Bond, L., Catroppa, C., Grimwood, K., Keir, E, Nolan, T. Childhood bacterial meningitis: Impact of age at illness and acute medial complication on long term outcome. *J International Neuropsychological Society* 1997 3, 147-158.

(24) Bittigau, P., Sifringer, M., Felderhoff-Mueser, U., Ikonomidou, C. Apoptic neurodegenration in the context of traumatic injury to the developing brain. *Experimental and Toxicologic Pathology* 2004; 56, 83-89.

(25) Dennis, M. Language and the young damaged brain. In T. Boll & Bryant (Eds.), *Clinical neuropsychology and brain function: Research, measurement and practice* (p.89-123). 1989. Washington: American Psychological Association.

(26) Schwartzkroin, P. Plasticity and repair in the immature central nervous system. In: *Brain Development and Epilepsy*: Schwartzkroin, P., Moshé, S., Noebels, J & Swann, J., (Eds.). p. 234-267. Oxford Univ. Press, New York.

(27) Anderson, V., Spencer-Smith, M., Coleman, L., Anderson P., Williams, J., Greenham, M., Leventer, R., Jacobs, R. Children's executive functions: Are they poorer after very early brain insult. *Neurospsychologia* 2010; 48, 2041-2050.

(28) Grigonis, A., Murphy, E. The effects of epileptic cortical activity on the development of callosal projections. *Developmental Brain Research* 1994; 77, 251-255.

(29) Thomas, M., Johnson, M. New advances in understanding sensitive periods in brain development. *Current Directions in Psychological Science* 2008; 17-1, 1-5.

(30) Kubova. H., Druga, R., Lukasiuk, K., Suchomelova, L., Haugvicova, R., Jirmanova, I., Pitkanen, A. Status epilepticus causes necrotic damage in the mediodorsal nucleus of the thalamus in immature rats. *Journal of Neuroscience* 2001; 21-10, 3593-3599.

(31) Wasterlain, C. Effects of neonatal status epilepticus on rat brain development. *Neurology* 1976; 26-10, 975-986.

(32) Corsellis, J., Burton, C. Neuropathology of status epilepticus in humans. In A.V. Deglado-Escueta, C. Wasterlain, D. Treiman & R. Porter (Eds.), *Status epilepticus:*

Mechanisms of brain damage and treatment. Advances in Neurology, vol. 34 (p. 129-139). New York: Raven Press.

(33) Fujikawa, D., Itabasji, H., Wu, A., Shinmei, S. Status epilepticus-induced neuronal loss in human without systematic complications or epilepsy. *Epilepsia*, 41-8, 981-991.

(34) Scott, R., Gadian, D., King, M., Chong, W., Cox, T., Neville, B. Connelly, A. Magnetic resonance imaging findings within 5 days of status epilepticus in childhood. *Brain* 2002; 125-9, 1951-1959.

(35) Aicardi, J., Baraton, J. A pneumoencephalographic demonstration of brain atrophy following status epilepticus. *Development Medicine Child Neurology* 1971; 13, 660-667.

(36) Meldrum, B., Brierley, J. Prolonged epileptic seizures in primates: ischaemic cell change and its relation to ictal physiological events. *Archives in Neurology* 1973; 28, 10-17.

(37) Wolf, O., Dyakin, V., Patel, A., Vafasz, C., De Leon, M., McEwen, B., Bulloch, K. Volumetric structural magnetic resonance imaging (MRI) of the rat hippocampus following kainic acid (KA) treatment. *Brain Research* 2002; 934-2, 87-96.

(38) Nairismagi, J., Pitkanen, A., Kettunen, M., Kauppinen, R., Kubova, H. Status epilepticus in 12-day-old rats leads to a temporal lobe neurodegenration and volume reduction: A histologic and MRI study. *Epilepsia* 2006; 47-3, 479-488.

(39) Niessen, H., Angenstein, F., Vielhaber, S., Frisch, C., Kudin, A., Elger, C., Heinz, H., Scheich, H., Kunz, W. Volumetricmagnetic resonance imaging of functionally relevant structural alterations in chronic epilepsy after Pilocarpine-induced status epilepticus in rats. *Epilepsia* 2005; 46-7, 1021-1026.

(40) Scantlebury, M., Heida, J., Hasson, H., Veliskova, J., Velisek, L., Galanopoulou, A., Moshé, S. Age-dependent consequences of status epilepticus: Animal models. Epilepsia 2007, 48-S2, 75-82.

(41) Ericson, E., Samuelsson, J., % Alhenius, S. (1991). Photocell measurements of rat motor activity. A contribution to sensitivity and variation in behavioral observation. *J. Pharmacol. Meth*, 1991; 25, 111-122.

(42) Kubova, H., Mares, P., Suchomelova, L., Brozek, G., Druga, R., Pitkanen, A. Status epilepticus in immature rats leads to behavioural cognitive impairment and epileptogenesis. *European Journal of Neuroscience* 2004; 19, 3255-3265.

(43) Muller, C., Groticke, I., Bankstahl, M., Loscher, W. Behavioral and cognitive alterations, spontaneous seizures, and meuropathology developing after a pilocarpine-induced status epilepticus in C57Bl/6 mice. *Experimental Neurology 2009*; 219-1, 284-297.

(44) Dos Santos, N., Arida, R., Filho, E., Priel, M., Cavalheiro, E. Epileptogenesis in immature rats following recurrent status epilepticus. *Brain Research Reviews* 2000; 32, 269, 276.

(45) Majak, K., Pitkanen, A. Do seizures cause irreversible cognitive damage? Evidence from animal studies. *Epilepsy & Behavior* 2004; 5, S35-S44.

(46) Hort, J., Brozek, G, Komarek, V., Langmeier, M., Mares, P. Interstrain differences in cognitive functions in rats in relation to status epilepticus. *Behavioural Brain Research* 2000; 112, 77-83.

(47) Koflen, W., Pehle, K., Konig, S. Is the long-term outcome of children following febrile convulsions favorable? *Developmental Medicine and Child Neurology* 1998; 40, 667-671.

(48) Dam, M. Children with epilepsy: The effect of seizures, syndromes, and etiological factors on cognitive functioning. *Epilepsia* 1990; 31-4, S26-S29.

(49) Van Esch, A., Ramlal, I., Van Steensel-Moll, H., Steyerberg, E., Derksen-Lubsen, G. Outcome after febrile status epilepticus. Developmental Medicine and Child *Neurology* 1996; 38, 19-24.

(50) Aicardi, J., Chevrie, J. Convulsive status Epilepticus in Infants and Children a Study of 239 Cases. *Epilepsia* 1970; 11, 187-197.

(51) Yager, J., Cheang, M., Seshia, S. Status Epilepticus in Children. *Canadian Journal of Neurological Science* 1988; 15, 402-405.

(52) Lacroix, J., Deal, C., Gauthier, M., Rousseau, E., Farrell, C. Admissions to a pediatric intensive car unit for status epilepticus: a 10-year experience. *Critical Car Medicine* 1994; 22-5, 827-832.

(53) Roy, H., Lippé, S., Lussier, F., Sauerwein, H., Lortie, A., Lacroix, J., Lassonde, M. Developmental outcome after a single episode of status epilepticus. *Epilepsy & Behavior* 2011; 21, 430-436.

(54) Diamond, A., Goldman-Rakic, P. Comparative development in human infants and infant rhesus monkeys of cognitive functions that depend on the prefrontal cortex. *Soc. Neurosci. Abst*., 12, 742.

(55) Fuster, J. Frontal lobe and cognitive development. *Journal of Neurocytology* 2002; 31-3-5, 373-385.

(56) Teffer, K., Semendeferi, K. Human prefrontal cortex: Evolution, development and pathology. *Prog Brain Res* 2012; 195, 191-218.

(57) Adachi, N., Kanemoto, K., Muramatsu, R., Kato, M., Akanuma, N., Ito, M., Kawasaki, J., Onuma, T. Intellectual Prognosis of Status Epilepticus in adult epilepsy patients: Analysis with Wechsler Adult Intelligence Scale-Revised. *Epilepsia* 2005; 49-9, 1502-1509.

(58) Dodrill, C., Wilensky, A. Intellectual impairment as an outcome of status epilepticus. *Neurology* 1990; 40-5, 25-27.

(59) Van Paesschen, W., Porke, K., Fannes, K., Vandenberghe, R., Palmini, A., Van Laere, K., Dupont, P. Cognitive deficits during status epilepticus and time course of recovery: a case report. *Epilepsia* 2007; 48-10, 1979-1983.

(60) Eriksson, K., Koivikko, M. Status epilepticus in children: aetiology, treatment and outcome. *Developmental Medicine and Child Neurology* 1997; 39, 652-658.

(61) Raspell-Chavre, M., Chin, R., Neville, B., Scott, R. Outcome of paediatric convulsive status epilepticus: a systematic review. *Lancet Neurology* 2006; 5, 769-779.

(62) Maytal, J. & Shinnar, S. Febrile Status Epilepticus. *Pedatrics* 1990; 86, 611-616.

(63) Aicardi, J. *Epilepsy in Children*. New York: Raven Press, 1986; 17-182.

(64) DeGiorgio, C., Gott, P., Rabinowicz, A., Heck, C., Smith, T, Correlale, J. Neuron-Specific Enolase, a marker of acute neuronal injury, is increased in complex partial status epilpeticus. *Epilepsia* 1996; 37-7, 606-609

(65) AicardJ. Amsili, J., Chevrie, J. Acute hemiplegia in infancy and childhood. *Develop Med Child Neurol* 1969; 11, 162-173

(66) Meldrum, B. Metabolic factors during prolonged seizures and their relationship to nerve cell death, In: Delgado-Escueta, A., Waterlain, C., Treiman, D., Porter, R. (Eds.) *Status*

Epilepticus: Mechanisms of brain damage and treatment. 1982. New York: Raven Press 1983; 261-275.

(67) Gross-Tsur, V. & Shinnar, S. Convulsive status epilepticus in chidren. *Epilepsia* 1993; 34-1, S12-S20.

(68) Shinnar, S., Maytal, J., Krasnoff L., Moshe, S. Recurrent Status Epilepticus in children. *Ann Neurol* 1992; 31, 598-604.

(69) Kotagal, P., Rothner, D., Erenberg, G., Cruse, R., Wyllie, E. Complex partial seizures of childhood onset: a five-year follow-up study. *Arch of Neurol* 1987; 44-11, 1177-1180.

(70) Holmes, G., Ben-Ari, Y. The neurobiology and consequences of epilepsy in the developing brain. *Pediatr Res* 2001; 49, 320-325.

(71) A., Cantu-Reyna, G., Stuss, D.m Broughton, R. Nonconvulsive generalized status epilepticus: Clinical features, neuropsychological testing and long-term follow-up. *Neurology* 1986, 36-10, 1284.

(72) Hermann, B., Jones, J., Jackson, D., Seidenberg, M. Starting at the beginning: the neuropsychological status of children with new-onset epilepsies. *Epileptic Disord* 2012; 14(1), 12-21.

(73) Guberman Holmes, G. Effects of seizures on brain development: Lessons from the laboratory. *Pediatr Neurol* 2005; 33, 1-11.

(74) Stores, G. Effects on learning of "subclinical" seizure discharge. In: Aldenkamp, AP, Meinardi, H, Stores, G. eds. *Education and epilepsy*. Lisse: Swets and Zeitlinger, 1987, 14-21.

(75) Singh RK, Stephens S, Berl MM, Chang T, Brown K, L. Gilbert Vezina LG, Gaillard WD. A prospective study of new onset seizures presenting as status epilepticus in

childhood, *Neurology* 2010, *74*, 636-642.

(76) Duffy, S. Craddock, K. Abel, T. Nguyen, P. Environmental enrichment modifies the PKA-dependence of hippocampal LTP and improves hippocampus-dependent memory. *Learn Mem* 2001, 8, 26-34.

(77) Towne, A., Pellock, J., Ko, D., DeLorenzo, R. Determinants of mortality in status epilepticus. *Epilepsia* 1994; 35-1, 27-34.

(78) Deonna, T. Cognitive and behavioral disturbances as epileptic manifestations in children: an overview. Seminars in Pediatric Neurology 1995; 2-4, 254-260.

(79) Stores, G., Williams, P., Styles, E., Zaiwalla, Z. Psychological effects of sodium valproate and carbamazepine in epilepsy. *Arch Dis Child* 1992; 67, 1330-1337.

(80) Elterman, R., Glauser, T., Wyllie, E., et al. A double-blind, randomized trial of topiramate as adjunctive therapy for partial-onset seizures in children. Topiramate YP Study Group. *Neurology* 1999; 52, 1338-1344.

(81) Wirrell, E., Farrell, K., Whitting, S. The epileptic encephalopathies of infancy and childhood. *Can. J. Neurol. Sci.* 2005; 32, 409-418.

(82) Manning, R. Non-convulsive Status Epilepticus. *Arch Dis Child* 1987; 62, 37-40.

(83) Halonen, T., Nissinen, J., Pitkanen, A. effect of lamotrigine treatment on status epilepticus-induced neuronal damage and memory impairment in rat. *Epilepsy Res* 2001; 46, 205-223.

(84) Hoffman, A., Zhao, Q., Holmes, G. Cognitive impairment following status epilepticus and recurrent seizures during early development: support for the "two-hit hypothesis". *Epilepsy and Behavior* 2004; 5, 873-877.

(85) Verity, C., Greenwood, R., Golding, J. Long-term intellectual and behavioral outcomes of children with febrile convulsions. *New England Journal of Medicine* 1998; 338-24, 1723-1728.

ARTICLE 2

COGNITIVE DEVELOPMENT IN CHILDREN PRESENTING WITH A COMPLEX FEBRILE SEIZURES: AT ONSET AND SCHOOL-AGE

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ABSTRACT

Objective: The aim of the current study was to assess development and cognition following an initial complex FS, at onset and school-age, in the context of known risk factors for poor outcome.

Methods: Two groups of participants were recruited transversally. Thirty-five infants presenting with an initial complex febrile seizure were assessed within the first year post seizure-onset and compared to thirty controls of similar demographics, on measures of cognitive, motor and language development, as well as on measures of behavior and emotion. Additionally, twenty-one school-age children having suffered complex FS were assessed and compared to nineteen children having suffered simple febrile seizures of similar demographics. Assessment was completed using an extensive and comprehensive neuropsychological battery of tests, including measures of intelligence, learning/memory and executive functioning, as well as measures of behavior and emotion.

Results: Infants having suffered a complex FS did not significantly differ on developmental measures as compared to controls, within the first year-post onset. Seizure duration and age at seizure onset did not impact developmental outcome. School-age children having suffered complex FS showed unaltered global intelligence as compared to simple FS controls. These children, including those having suffered prolonged and multiple seizures, however showed significantly weaker executive functioning, learning and memory as compared to controls. Scores worsened as a function of seizure duration. Emotionally, children having suffered complex FS scored worse on measures of attention problems, anxious/depressed

symptomology and affective problems, across both cohorts. School-age children additionally scored higher on a scale of hyperactivity, as measured by parental questionnaires. Earlier ages of onset were associated with increased perfectionism traits.

Conclusion: Infants having suffered an initial complex FS showed normal development within the first year-post seizure onset, whereas school-age children demonstrated challenges in specific cognitive domains, including executive functioning, learning and memory. As such, children may demonstrate cognitive challenges at school-age, even though early cognitive development is undifferentiated. These challenges may occur even without presenting with the most severe form of FS (i.e., FSE). Follow-up regarding the impact of complex FS on cognition is however necessary beyond the developmental years and into adolescence, in order to understand their long-term outcome.

KEY WORDS: Febrile seizure; Complex febrile seizure; Development; Cognition; Behavior; Infant; Children

INTRODUCTION

Febrile seizures (FS) are defined as a seizure in association with a febrile illness, in the absence of a central nervous system infection or acute electrolyte imbalance in children older than 1 month of age, without prior afebrile seizures (ILAE, 1993). They are the most common form of childhood seizures, affecting 2% to 5% of children between the ages of 6 months and 5 years (Verity et al., 1985; 1998; Leung & Robson, 1991; Berg & Shinnar, 1996; Shinnar &

Glauser, 2002; Stafstrom, 2002). Simple FS are characterized by a brief (less than 10 minutes), isolated and generalized seizure episode. Complex FS occur in approximately 20% of children presenting with FS, and are arguably more severe. They are characterized by either a prolonged (lasting between 15 and 30 minutes), recurrent within the same febrile illness, or focal seizure episode, or a combination of complex features. Febrile status epilepticus (FSE) is a subtype of complex febrile seizure, in which the seizure persists for at least 30 minutes (Maytal & Shinnar, 1990; Berg & Shinnar, 1996). Although converging evidence from multiple studies has revealed the benign nature of simple FS, demonstrating outcomes similar to otherwise healthy developing children (Steering Committee on Quality Improvement Management, 2008; Shinnar, 2012), outcomes subsequent to complex FS have been controversial, and remain a matter of on-going debate.

Prolonged FS and FSE have been linked to structural anomalies in the developing brain. In particular, these types of FS have been linked to acute hippocampal injury leading to mesial temporal sclerosis (Provenzale, 2008; Shinnar, 2003; Shinnar et al., 2012; Lewis et al., 2014). They have also been linked to an increased risk of developing mesial temporal lobe epilepsy as compared to the general population (Davis et al., 1996; Cendes et al., 1993).

Few studies to date have investigated the impact of FS on development within the first year-post onset. Infants having suffered very prolonged FS, that is, Febrile Status Epilepticus (FSE) have been shown to develop normally within the first month post-seizure onset, although demonstrated slightly weaker motor development and receptive language one year-post onset (Weiss, 2016). Children having suffered a very prolonged complex FS similarly demonstrated

worse developmental outcome as compared to controls 6 weeks and 1 year following seizure onset (Martinos, 2013), as well as accelerated forgetting within the first month and 1 year following onset (Martinos, 2012). Weaker development one year-post onset has further been linked to hippocampal anomalies in children having suffered prolonged seizures (Weiss, 2016; Martinos, 2012). Taken together, these results suggest a possible worsening of the impact of an initial very prolonged seizure, that is, lasting between 70 and 90 minutes, on development over time. This proposed weakening outcome within the first year post-onset however requires to be further investigated, particularly considering other complex FS features, in order to better differentiate their impact on development.

Beyond the early stages of development, large epidemiological studies have generally showed unaltered global intelligence, scholastic achievement and academic skills in school-age children following FS (Ellenberg & Nelson, 1978; Verity et al., 1998; Hirtz, 2002). Several methodological caveats of these studies have however been noted, including the lack of specificity and objectivity of the measures used. In accommodating these psychometric weaknesses, other studies have revealed contrasting evidence regarding the impact of complex FS on cognition and behavior in school-age children, although discrepancies in methodologies are further noted, including populations used (i.e., population versus hospital-based samples), complex seizure type studied (i.e., prolonged versus multiple versus focal), measures used (i.e., objective versus subjective) and time points assessed (i.e., varying time points since seizure onset or last seizure occurrence) (Kolfen et al., 1998; Chang et al., 2000; Chang et al., 2001; Norgaard et al., 2009; Visser et al., 2012). Moreover, these studies lacked the

assessment of specific cognitive functions, even though these functions have sufficiently differentiated in school-age children to allow their evaluation in relative isolation.

Few studies to date have investigated isolated cognitive functions in this population. These studies have focused on the assessment of hippocampus-dependent cognitive functions, such as learning and memory, given the association between prolonged FS/ FSE and hippocampal damage (Cendes et al., 1993; Davis et al., 1996; Lewis et al., 2014). In particular, school-age children having suffered non-prolonged complex FS demonstrated similar performances as compared to controls on computerized memory tasks, although the mechanisms used to achieve similar behaviors were different, as evidenced by altered event-related potentials and hemodynamic activity (Kipp et al., 2010; 2012). Although the hippocampus is argued to be the most affected structure in prolonged FS and FSE, very little research has been performed in investigating hippocampal abnormalities in the context of larger cerebral networks, including the cortico-hippocampal network. A more exhaustive investigation of the impact of FS on specific cognitive functions, beyond hippocampus-dependent capacities, has yet to be done.

Given the connections between the hippocampus and frontal/prefrontal areas, including the medial prefrontal cortex known for its involvement in executive functioning, these capacities may be targeted following complex FS (Miller, et al., 1991; Jay, et al., 1992; Thierry, et al, 2000; Petrides & Pandya, 2004; Brassen 2006). Indeed, executive functions are known to be vulnerable to neurodevelopmental conditions and disorders (Ozonoff et al., 1999; Shanmugan, 2016), but are crucial for academic performance. To date, few studies have investigated the impact of FS on executive functioning in school-age children, and evidence thus far has been

controversial. While some studies suggest that complex FS are associated with increased external behavioral deficits and increased attentional difficulties as measured by parental questionnaires (Kolfen et al., 1998; Lippé et al., 2009; Tsai et al., 2015), other studies have demonstrated no impact of complex FS on executive function as measured by questionnaires (Visser et al., 2012). When using objective measures, evidence has been found for weaker sustained attention abilities in children having suffered complex FS (Hara et al., 1986), whereas findings from two large population-based studies demonstrated better performances on measures of working memory in children having suffered FS (Chang et al., 2000; 2001). Of note, the two latter studies arguing for better performances in children having suffered FS, concluded as such based on their findings that these children performed better than controls at sustaining their attention on challenging tasks, although their results demonstrate that they had more difficulty than controls sustaining their attention on simple tasks, which could possibly indicate a need for arousal and challenges in self-monitoring abilities. These contrasting findings related to executive function are also a result of methodological inconsistencies.

To our knowledge, no study has yet assessed learning, memory and the spectrum of executive functions using specific and objective neuropsychological measures in children having suffered complex FS, particularly in the context of known risk factors for poor outcome.

Several risk factors have been identified for febrile seizure recurrence, including early age at onset, history of at least one complex FS feature, and prolonged FS duration (Wilmhurst et al., 2015; Hesdorffer et al., 2016; Patel & Perry, 2017). The impact of these identified risk factors for seizure recurrence on other aspects of outcome, including cognitive development, however

remains unclear. Studies to date have similarly revealed contrasting evidence regarding the relationship between these seizure characteristics and outcome, although study groups are often defined by strict criteria, forgoing the variability required to detect the potential impact (e.g., when experimental groups are defined by prolonged seizures, there is too little variability in seizure duration to detect its impact on outcome).

The objective of the current study was to investigate development and cognition from onset to school-age following complex FS, as compared to children having suffered simple FS, in the context of known risk factors for poor outcome, including all types of complex features. More specifically, we aimed to transversally evaluate development within the first year-post seizure onset, as well as cognition in a cohort of children old enough for cognitive functions to be sufficiently differentiated (i.e., school-age).

METHODS

Participants

Two cohorts of participants were transversally recruited retrospectively. Infants were recruited at the onset of their first seizure (i.e., Infant Cohort), and children were recruited at the beginning of their schooling, namely between five and six years of age (i.e., School-Age Cohort). In both cohorts of participants, infants/children having suffered complex febrile seizures (experimental group) were compared to infants/children having suffered a simple febrile seizure (control group) of similar demographics, given their known benign outcome. As such, recruitment for both groups in both cohorts was completed similarly, that is, through

the Child University Hospital Center Sainte-Justine's (CHU Sainte-Justine) Emergency Department. The study was approved by the hospital's research ethics board.

A simple febrile seizure was defined as a generalized seizure lasting less than 10 minutes, without recurrence of seizure within the same episode of fever. This was the inclusion criteria for the control group. A complex febrile seizure was defined either as a seizure with focal onset (i.e., focal complex febrile seizure), occurring more than once in the same episode of fever (i.e., multiple complex febrile seizure), and/or lasting more than 15 minutes (i.e., prolonged complex febrile seizure), or a combination of either complex criteria. Exclusion criteria for both groups included CNS infection, occurrence of afebrile seizures, epilepsy and known developmental delays. None of the participants were taking medication at the time of testing. Information pertaining to childrens' seizure and medical history were gathered through extensive review of their medical files, and consultation with a pediatric neurologist as necessary.

Infant Cohort

Infants aged 6 to 42 months having been discharged from the Emergency Department with a diagnosis of a first febrile seizure (either simple or complex) were flagged by ER physicians and nurses, and their parents were contacted by our research team for participation within one year-post seizure onset. 195 infants who were referred to our team through the Emergency Department were eligible to participate in the study, 33% of which parents accepted to participate. Thus, 35 infants (19 females; 16 males) were recruited as the experimental group (i.e., complex febrile seizures; 19 multiple, 10 prolonged, 6 focal), and 30 infants (16 females;

14 males) were recruited as the control group (i.e., simple febrile seizures). All participants' parents provided written informed consent to participate.

School-Age Cohort

ER physicians provided our research team with a list of school-age children having been discharged from the Emergency Department with a diagnosis of febrile seizure (either simple or complex) roughly 5 years prior, that is, between the ages of 6 and 42 months. Each of their medical files was extensively reviewed for eligibility to participate. Two hundred and twenty-three children were eligible to participate in the study, 17.9% of which parents accepted to participate. Thus, 21 children (9 females; 12 males) were recruited as the experimental group (i.e., complex febrile seizures; 11 multiple, 10 prolonged, 0 focal), and 19 children (11 females; 8 males) were recruited as the control group (i.e., simple febrile seizures). All participants' parents provided written informed consent to participate.

Procedures

Infant Cohort

After agreeing to participate, parents accompanied their infant to a testing appointment at CHU Sainte-Justine. Demographic information was collected through an in-house developmental questionnaire, thoroughly reviewed by the examiner with the family. Neuropsychological testing was completed in one session with two examiners who were Masters or Doctoral students in Neuroscience or Clinical Neuropsychology, who had received extensive training in the administration of the measures. The accompanying parent remained in the testing room, which would typically ease the infant and add comfort to the testing

environment. Behavioral questionnaires were completed by the parent either simultaneously or after the neuropsychological testing. Scoring was completed by both examiners together.

School-Age Cohort

After agreeing to participate, parents accompanied their child to a testing appointment at CHU Sainte-Justine. Demographic information was similarly collected through an in-house developmental questionnaire, thoroughly reviewed by the examiner with the family. Neuropsychological testing was completed and scored by a Doctoral student in Clinical Neuropsychology, who had received extensive training on the administration of the measures. Testing was done in one session, independently with the child. The order of the measures administered was the same for all participants and several breaks were scheduled in the testing session. Simultaneously, behavior questionnaires were completed by the accompanying parent.

All administration and scoring was overseen by a registered Neuropsychologist.

Measures

Infant Cohort

Infants' development was assessed using the Bayley Scales of Infant and Toddler Development, 3rd Edition (Bayley-III; Bayley, 2005), and behavioral and emotional problems were assessed using the Child Behavior Checklist for ages 1.5 to 5 years (CBCL; Achenbach & Rescorla, 2000).

Bayley Scales of Infant and Toddler Development, 3rd Edition

The Bayley-III is a comprehensive individually-administered test battery designed to assess the developmental functioning of infants between the ages of 1 and 42 months (Bayley, 2005). Age appropriate test items allowed to assess cognition, receptive and expressive communication, as well as fine and gross motor skills. Scaled scores with a mean of 10 and a standard deviation of 3 were obtained for each of the abilities assessed using age-matched norms of a general population sample. Moreover, composite scores for cognition, language and motor skills, with a mean of 100 and standard deviation of 15 were derived.

Child Behavior Checklist

The CBCL for ages 1.5 to 5 is a 99-item questionnaire filled out by primary caregivers designed to assess their infants' behavioral and emotional problems (Achenbach & Rescorla, 2000). Given the minimum age of 18 months required to complete the questionnaire, and the age range of our groups being 6 to 42 months, only a subgroup of our sample was able to complete the questionnaire. Specifically, the CBCL was completed for 14 participants in the complex group and 11 participants in the simple group. Results are organized according to seven syndrome scales; emotionally reactive, anxious/depressed, somatic complaints, withdrawn, sleep problems, attention problems and aggressive behavior, as well as five DSM-oriented scales; affective problems, anxiety problems, pervasive developmental problems, attention deficit/hyperactivity problems and oppositional defiant problems. Based on these results, three global indices are derived; Internal problem (derived from the emotionally reactive, anxious/depressed, somatic complaints, and withdrawn scales), External problems (derived from the attention problems and aggressive behavior scales), and Total problems

(derived from all scales combined). T-scores are provided for all scales and indices, based on age-matched norms of a general population sample; the higher the score, the more problematic are the behaviors.

School-Age Cohort

A comprehensive neuropsychological battery of tests was used to assess intellect, learning/memory and executive functioning. In particular, children's intellectual and general cognitive capacities were assessed using the Wechsler Preschool and Primary Scale of Intelligence, 3rd Edition (WPPSI-III; Wechsler, 2002). Learning and memory abilities were assessed using the California Verbal Learning Test for Children (CVLT-C; Delis et al., 1994), as well as selected subtests of the Developmental Neuropsychological Assessment, 2nd Edition (NEPSY-II; Korkman et al., 2007). Selected subtests of the latter test battery also allowed for the assessment of attention and executive functioning. Emotion and behavior were assessed by means of questionnaires completed by the parent, including the Conners' Parent Rating Scale Revised Long Form (Conners; Conners, 1997) and the Child Behavior Checklist (CBCL; Achenbach & Rescorla, 2000; 2001). All tests yielded standardized scores normed according to age-matched peers of a general population sample.

WPPSI-III

The WPPSI-III is a comprehensive individually-administered test battery designed to assess intelligence and general cognitive capacities in children between the ages of 2 years 6 months and 7 years 3 months. Selected subtests included Information and Vocabulary, which allowed the calculation of a prorated Verbal IQ Index, as well as Blocs and Matrices, which allowed

the calculation of a prorated Performance IQ Index. The administration of two additional subtests, namely Comprehension and Object Assembly, in combination with the four previously mentioned subtests allowed for the calculation of a prorated Global IQ Index. The Receptive Vocabulary subtest was also administered. Composite scores with a mean of 100 and a standard deviation of 15 were provided for each of the indices. Higher scores on these scales are representative of better capacities.

CVLT-C

The CVLT-C is an individually-administered test design to assess verbal learning over repeated trials, as well as memory of newly learned information in children and adolescents between the ages of 5 and 16 years. For the purposes of our study, we derived two scores from this test: a Learning score, derived from the child's ability to learn a list of words over five repeated trials, and a Recognition score, derived from the child's ability to recognize the newly learned information among distractors following a 20-minute delay. T-scores with a mean of 50 and a standard deviation of 10 were provided for each of the scores. The higher the scores, the better the participant's ability to learn and remember.

NEPSY-II

The NEPSY-II is a comprehensive individually-administered test battery consisting of 32 subtests designed to assess a wide range of cognitive capacities, including attention and executive functioning, language, social perception, visuospatial processing, memory and learning as well as sensorimotor functioning in children and adolescents between the ages of 3 and 16 years. For the purposes of the current study, selected subtests were chosen to assess

visual and verbal learning and memory, including Memory for Designs (visual memory), Narrative Memory (verbal memory) and Sentence Repetition (working memory). Specific subtests were also selected to assess attention and executive functioning, including Auditory Attention (selective and sustained attention), Inhibition (inhibitory capacities), Design Fluency (generation capacities) and Statue (hyperactivity). For each subtest, a scaled score with a mean of 10 and a standard deviation of 3 was provided. Higher scores on each scale represent better test performance.

Conners

The Conners Parent Rating Scale is an 80-item questionnaire filled out by primary caregivers designed to evaluate children and adolescents between the ages of 3 and 17 for Attention Deficit Hyperactivity Disorder (ADHD). Results are organized according to seven scales; Oppositional, Cognitive Problems/Inattention, Hyperactivity, Shy/Anxious, Perfectionism, and Psychosomatic. Several Index scores and DSM-IV subscale composites can be derived, although only scores related to the scales themselves were used for the purposes of the current study. T-scores were provided for each scale; the higher the score, the more participants display problematic behaviors in their daily lives.

CBCL

Two versions of the CBCL were utilized, dependent on the age of the child; CBCL for ages 1.5 to 5 and the CBCL for ages 6 to 18. The CBCL for ages 1.5 to 5 was previously described in the *Infant Cohort* measures. The CBCL version for ages 6 to 18 is a 113-item questionnaire filled out by primary caregivers, similarly designed to assess behavior and emotional

problems. The results are organized according to eight syndrome scales. Similarly to the 1.5-5 version of the questionnaire are the anxious/depressed, withdrawn, somatic complaints, attention problems, and aggressive behavior scales. Additionally, there are the social problems, thought problems, and rule-breaking behavior scales. Based on these results, three global indices are similarly derived; Internal problem (derived from the anxious/depressed, withdrawn and somatic complaints scales), External problems (derived from the rule-breaking behavior and aggressive behavior scales), and Total problems (derived from all scales combined). For all syndrome scales and indices, T-scores were provided; the higher the score, the more participants displayed problematic behaviors or emotions in their daily lives. This version of the questionnaire was completed by 12 participants in the complex group and 12 participants in the simple group.

Statistical Analyses

In both cohorts, data processing and statistical analyses were carried out using IBM Statistical Package for Social Sciences (SPSS) for Windows, Version 22.0 (IBM, Armonk, NY). Descriptive analyses were performed on both cohorts. Normality was examined using skewness and kurtosis values (i.e., $|0 - 3|$), as well as visual inspection of histograms and quantile-quantile plots. When necessary, variable distributions were transformed to normality using log transformations.

Developmental/Neuropsychological Measures

Infant Cohort

Demographic variables and seizure characteristics were compared between groups using chi-square tests for categorical variables (i.e., sex), and independent samples Student's T-tests for continuous variables (i.e., familial income, parent education, age at seizure onset, age at test, time between last seizure and test). Multivariate analysis of variance (MANOVA) was used to compare both groups on developmental measures (i.e., Bayley-III scaled scores for cognition, receptive and expressive communication, as well as fine and gross motor skills). Correlational analyses using Pearson's bivariate correlation were further completed to investigate the relationship between our study variables and seizure characteristics known to be risk factors for poorer outcome (i.e., age at seizure onset and seizure duration).

School-Age Cohort

Demographic variables and seizure characteristics were compared between groups using chi-square tests for categorical variables (i.e., sex), and one-way ANOVA for continuous variables (i.e., familial income, parent education, age at seizure onset, age at test). Given the similar sample size of multiple and prolonged seizures within our complex febrile seizure group, a one-way ANOVA was used to investigate group differences between multiple complex, prolonged complex as well as simple febrile seizures on a composite measure of global intelligence (i.e., composite Full Scale IQ score on the WPPSI-II). NEPSY-II and CVLT-C scores were transformed into two cognitive domains: Executive Functioning and Memory. The Executive Function domain included the pooled and weighted scores of the NEPSY-II Auditory Attention, Inhibition, Design Fluency and Statue subtests. The Memory domain included the pooled and weighted scores of the NEPSY-II Sentence Repetition subtest, as well as the CVLT-C learning and memory scores. Each domain was compared between groups

using repeated measures ANOVA, that is, GROUP (multiple, prolonged and simple FS) X COGNITIVE DOMAIN (executive functioning and memory). Significant interactions were explored using post-hoc ANOVAs. Correlational analyses using Pearson's bivariate correlation were further completed to investigate the relationship between our study variables and seizure characteristics known to be risk factors for poorer outcome (i.e., age at seizure onset and seizure duration).

Behavioral/Emotional Measures

Both cohorts combined

Since the CBCL was administered in both cohorts, the sample was pooled for statistical analysis. As such, scores of 34 children having suffered complex FS (mean age: 4.54 years old, SD: 1.83) were compared to scores of 30 children having suffered simple FS (mean age: 4.51 years old, SD: 2.0). Only scales available in both versions of the questionnaire were considered in the analysis. These CBCL scales were compared between cohorts and seizure type using MANOVA. Significant effects were followed up by post-hoc ANOVAs. Correlational analyses using Pearson's bivariate correlation were further completed to investigate the relationship between our study variables and seizure characteristics known to be risk factors for poorer outcome (i.e., age at seizure onset and seizure duration).

School-Age Cohort

MANOVA was used to compare behavior/emotion measures (i.e., scores on the Conners) between study groups. Significant MANOVAs were followed up by one-way ANOVAs and Bonferroni-corrected t-tests. Correlational analyses using Pearson's bivariate correlation were

further completed to investigate the relationship between our study variables and seizure characteristics known to be risk factors for poor outcome (i.e., age at seizure onset and seizure duration). In order to obtain a more detailed picture of these relationships, NEPSY-II and CVLT-C subtest scores were used for the correlations. Assumptions necessary to perform our planned statistical analyses were verified and satisfied.

RESULTS

Developmental/Neuropsychological Measures

Infant Cohort

Descriptive Statistics

Our complex FS group included thirty-five participants; 19 having suffered complex multiple FS, 10 having suffered complex prolonged FS, and 6 having suffered complex focal FS, which together were compared to our control group composed of 30 infants having suffered simple FS. In considering infants having suffered prolonged FS, the mean seizure duration was 27.3 minutes. In comparing infants having suffered complex versus simple seizures, T-tests revealed no significant group differences in demographics, including age, sex, familial income, and parent education, or in seizure characteristics other than characteristics defining both groups, including age at seizure onset, age at test and time between last seizure and test ($p > 0.09$) (Table 1).

[INSERT TABLE 1]

Developmental Results

Sixty-five infants completed the Bayley-III, 35 having suffered a complex seizure and 30 having suffered a simple seizure. Following the assessment of normality of variable distributions, log transformations were applied to the following study variables: time between last seizure and test, seizure duration, and Bayley-III motor and language composites.

Mean performances across all Bayley-III scales for both simple and complex FS groups fell within average ranges (Table 2). MANOVA comparing both groups showed no significant differences between complex and simple FS on developmental scores within the first year following seizure onset.

[INSERT TABLE 2]

Correlational analyses completed between study variables and seizure characteristics considered risk factors revealed no significant relationships between developmental scores and age at seizure onset and seizure duration. Similarly, no significant relationships were found between developmental scores and time between last seizure and test within the first year following seizure onset.

School-Age Cohort

Descriptive Statistics

Our experimental samples included a group of 11 children having suffered complex multiple FS, and a group of 10 children having suffered complex prolonged FS, which were compared

to 19 simple FS controls. In considering our prolonged group, mean seizure duration was 19.5 minutes. One-way ANOVA revealed no significant differences in demographics between children having suffered a complex prolonged, complex multiple or simple FS, including familial income, parent education and gender, or in seizure characteristics other than characteristics defining both groups, including age at seizure onset and age at test ($p > 0.14$) (Table 3).

[INSERT TABLE 3]

All forty children completed all measures, although two participants were removed from the analyses given that they had suffered both prolonged and multiple seizures. As such, included in our groups were 8 children having suffered a complex prolonged seizure, 11 children having suffered a complex multiple seizure, and 19 children having suffered a simple seizure.

Neuropsychological Results

One-way ANOVA comparing children having suffered a complex prolonged, complex multiple and simple seizure revealed no significant differences between groups on measures of intelligence (Table 4). Repeated measures ANOVA revealed a significant interaction between cognitive domain (executive functions vs. memory) and seizure type (prolonged complex vs. multiple complex vs. simple FS) ($F(2, 35) = 12.78$, $p = 0.000068$). A main effect of cognitive domain ($F(1, 35) = 56.04$, $p = 0.00000001$) and a seizure type group effect ($F(2, 35) = 44.48$, $p = 0.0000000002$) were also found. Post-hoc ANOVAs revealed that there was a significant difference in performance between cognitive domains in both complex FS groups (multiple

complex FS: ($F(1, 10) = 25$, $p = 0.001$), prolonged complex FS: ($F(1, 7) = 21.28$, $p = 0.002$)), but not in the simple FS group (($F(1, 18) = 1.12$, $p = 0.303$) (Table 4). Both complex FS groups showed significantly worse performance in executive functions (multiple complex FS: M = 6.93, SD = 1.72; prolonged complex FS: M = 6.5, SD = 1.72) compared to memory (multiple complex FS: M = 10.42, SD = 1.65; prolonged complex FS: M = 10.25, SD = 1.59) (Figure 1). Finally, Bonferroni-corrected post-hoc t-tests between seizure groups revealed significantly lower scores for both cognitive domains in the complex FS seizure groups when compared to the simple FS group ($p < 0.013$).

[INSERT TABLE 4]

[INSERT FIGURE 1]

Correlations between executive functions/ memory domains and seizure characteristics considered risk factors revealed significant negative correlations between seizure duration and both cognitive domains (executive functions: $r = -0.560$, $p = 0.0002$; memory: $r = -0.391$, $p = 0.013$). These two correlations did not significantly differ from each other ($z = -1.215$, $p = 0.22$), meaning that the correlation between seizure duration and executive functions is not necessarily stronger than the one between seizure duration and memory. Follow-up correlations between seizure duration and specific subtests revealed significant correlations between seizure duration and measures of attention and executive functioning, including NEPSY-II Auditory Attention ($r = -0.612$, $p = 0.0001$), Inhibition ($r = -0.407$, $p = 0.009$), and Statue ($r = -0.686$, $p = 0.0001$) (Figure 2), as well as on measures of learning and memory,

including NEPSY-II Narrative Memory Learning (r = -0.495, p = 0.001) and Narrative Memory Recognition (r = -0.481, p = 0.002) (Figure 3). These results suggest that as seizure duration increased, performance on these measures decreased. There were no significant relationships between neuropsychological scores and age at seizure onset.

[INSERT FIGURE 2]

[INSERT FIGURE 3]

Behavioral/Emotional Measures

Both cohorts combined

Mean performances across all CBCL scales for both simple and complex FS groups across both cohorts fell below clinically significant cutoffs (Table 5). MANOVA nevertheless revealed a significant effect of seizure type on CBCL scales (F(9, 52) = 2.4, p = 0.023). No main effect for age group or interaction between seizure type and age group was found. Post-hoc ANOVAs revealed CBCL scales of Attention deficit/ hyperactivity problems (F(1, 60) = 4.81, p = 0.032), anxious/depressed (F(11, 60) = 8.08, p = 0.006) and attention problems (F(1, 60) = 4.45, p = 0.039) to differ between seizure type, with the complex FS group presenting higher scores than the simple FS group (Figure 4).

[INSERT TABLE 5]

[INSERT FIGURE 4]

Correlational analysis revealed no significant relationships between CBCL scores and age at seizure onset or seizure duration for the entire sample.

School-Age Cohort

MANOVA comparing Conners subscales between children having suffered a complex prolonged, complex multiple and simple seizure revealed a significant effect of seizure type on Conners measures ($F(10, 62) = 2.05$, $p = 0.043$). Bonferroni-corrected post-hoc ANOVAs showed a significant difference on a measure of executive functioning, namely the Conners Hyperactivity scale ($F(2, 34) = 5.72$, $p = 0.007$). Bonferroni corrected post-hoc t-tests showed that children having suffered complex multiple seizures ($p = 0.008$) scored worse than children having suffered complex prolonged or simple FS controls (Table 6). Of note, children in all groups across all behavior/emotion scales scored below clinical cutoffs.

[INSERT TABLE 6]

Correlations between study variables and seizure characteristics considered risk factors revealed significant negative correlations between age at seizure onset and Conners Perfectionism scale ($r = -0.565$, $p = 0.0001$), suggesting that a younger age at onset was associated with higher perfectionism traits (Figure 5). There were no significant relationships between behavior/emotion scores and seizure duration.

[INSERT FIGURE 5]

DISCUSSION

The aim of the current study was to examine cognition and behavior following an initial complex FS and at school-age. In particular, we aimed to investigate infants and toddlers within the first year-post onset. Furthermore, we aimed to investigate the impact of complex FS on the development of specific cognitive functions, including learning, memory and executive functioning, at an age when these capacities have begun differentiating (i.e., school-age children). Moreover, we aimed to evaluate the impact of FS on development and cognition in the context of known risk factors (i.e., age at seizure onset, seizure duration and other complex FS features).

Our results revealed no differences in developmental outcome within the first year post-seizure onset, including cognitive, language and motor development, between infants having suffered complex versus simple FS. Infants having suffered a complex FS overall performed within average ranges across developmental measures, similarly to infants having suffered a simple FS. These results are consistent with previous findings showing developmental scores within average ranges at baseline and one year post-onset in infants having suffered prolonged FS/ FSE (Martinos, 2013; Weiss, 2016). These previous findings also revealed no impact of the initial seizure on development at one month post-onset, although demonstrated slightly weaker performances in motor development and receptive language in infants having suffered very prolonged seizures one year-post onset (Weiss, 2016).

At school-age, our results revealed no significant differences in global intellectual capacities between children having suffered complex FS and simple FS controls, consistent with the existing literature (Ellenberg & Nelson, 1978; Verity et al., 1998; Hirtz, 2002). School-age children having suffered complex FS, however, demonstrated significantly weaker executive functioning, and to a lesser extent, learning and memory as compared to simple FS controls. Our results objectively corroborate those of previous studies indicating increased external behavior deficits and increased attentional difficulties in school-age children following complex FS, as measured by parental questionnaires (Lippé et al., 2009; Tsai et al., 2015). This contrasts with another study that found no differences between children having suffered FS and healthy controls on questionnaires (Visser et al., 2012). Of note, the latter study defined their FS group by its general definition, and did not account for possible differences between simple and complex seizures. Moreover, in the context of previous studies that used objective measures, our results are consistent with those of Hara et al., (1986) that similarly revealed sustained attention difficulties in children having suffered FS.

Furthermore, children having suffered a complex FS showed significantly weaker performances on learning and memory tasks as compared to simple FS controls. These results are consistent with previous findings demonstrating a negative impact of prolonged FS or febrile status epilepticus on memory functions, including recognition memory, which was further associated with hippocampal anomalies (Martinos et al., 2012; Weiss et al., 2016). Of note, our results showed that memory capacities were affected to a lesser degree than executive functions, which can be surprising given the importance of the hippocampus in FS, as highlighted by animal models and early human imaging studies. It is however important to

note that these studies restricted their clinical sample to very prolonged seizures and FSE, in contrast to the participants included in the current study. Moreover, these studies focused on hippocampal anatomy and the assessment of hippocampal-dependent cognitive functions (e.g., the Morris Water Maze in animal models and computerized memory tasks in humans). Imaging and other anatomy analysis techniques have yet to be done beyond the mesial temporal lobe. This could be interesting in future, given the numerous connections between the hippocampus and other brain structures. In particular, the cortico-hippocampal network plays a predominant role in learning and memory. Based on the current results, it can be speculated that early damage to the hippocampus may result in faulty connections in this network, decreasing its efficiency and hindering its function beyond functions that are strictly hippocampus-dependent.

With regards to behavioral and emotional problems, our results indicated significant parental concern regarding attention problems, anxious/depressed symptomology and affective challenges in children having suffered complex FS from onset to school-age. Heightened hyperactivity was also noted by parents of children having suffered complex FS. These results are commensurate with previous findings demonstrating weaker attentional abilities as observed through parental questionnaires (Lippé et al., 2009; Tsai et al., 2015). Scores across all scales nevertheless remained within normal ranges for both groups across both cohorts, consistent with previous findings showing normal behavioral and emotional functioning in early life (Verity et al., 1998; Visser et al., 2012). In considering risk factors, our results showed no impact of seizure duration and age at seizure onset on behavior and emotion, commensurate with previous findings showing negligible associations between seizure

characteristics and outcome (Martinos et al., 2012; Weiss et al., 2016). Overall, parents of children having suffered complex FS seem to show significant concerns related to behavior and emotion as compared to parents of children having suffered simple FS, even though these concerns are within normal ranges. Given the subjective nature of these measures, our results reflect behavioral issues as observed by the parent. As such, we cannot rule out the possible impact and influence of parental stress on our results. In considering this potential confound, it is possible that parents who are stressed as a result of the FS event have a biased perception of their child's skills, although children with weaker skills can also lead to parental stress. Results on the questionnaire may also reflect a bidirectional relationship between parental stress and children with weaker skills. At school-age more specifically, high scores on the hyperactivity scale are consistent with our neuropsychological measures, although overall parental behavior ratings seem to underestimate the amplitude of the measured objective neuropsychological challenges, notably related to executive functioning. Overall, given the caution required in interpreting results from parental questionnaires, behavioral and emotional challenges following FS remain unclear and require further research.

In considering known risk factors for poor outcome, our results revealed no impact of age at seizure onset or seizure duration on developmental outcome within the first year-post onset. In previous studies, only infants having suffered very prolonged seizures or FSE were included in clinical samples, whereas the current study aimed to include different types of complex features. In considering our participants that met criteria for prolonged complex FS, the mean seizure duration was 27.3 minutes, whereas mean seizure duration in previous studies was between 70 and 90 minutes (Weiss, 2016; Martinos, 2012). As such, it is possible that FS

meeting complex criteria, without meeting criteria for FSE, are not sufficiently severe to alter developmental trajectories within the first year-post onset. At school-age however, seizure duration was significantly associated with measures of executive functioning (i.e., attention, inhibition, generation and hyperactivity) and learning and memory. In considering the school-age children that met criteria for prolonged complex FS, the mean seizure duration was 19.5 minutes, suggesting that the observed cognitive challenges are of concern for children presenting with prolonged seizures, even before they meet criteria for FSE. Moreover, early age at seizure onset was associated with emotional anomalies (i.e., perfectionism) in school-age children, although limitations related to parental questionnaires must continue to be considered.

Overall, the impact of known risk factors appears minimal, or remains undetected by our measures, within the first year-post onset, although the impact of seizure duration on executive functioning and learning and memory are apparent at school-age. In the context of existing literature however, it seems as though children having suffered very prolonged seizures or FSE already demonstrate early gaps in developmental trajectories as compared to controls, which continue to persist and exacerbate through time. Indeed, it has been argued that outcome following FSE is related to more than just the seizure event itself, but rather to the impact of combined predispositions and environmental circumstances (Baulac et al., 2004; Lucas et al., 2011; Martinos et al., 2012). Nevertheless within our clinical sample that did not include FSE, our results indicate that seizure characteristics known to be risk factors seem to be associated, at least in part, with outcome (i.e., seizure duration related to behavioral outcome and age at onset related to internal emotional problems). These results persist, even

when controlling for confounding variables unrelated to the seizure event, but known to be associated with poor cognitive outcome following FS, including pre-existing developmental issues, pre-existing CNS lesions and socio-economic status (i.e., familial income and parental education). As such, our significant associations between seizure characteristics and outcome could indicate that problems and deficits observed in behavior and emotion could, at least in part, be an effect of the seizure per se.

Taken together, our results suggest that infants having suffered complex FS demonstrate unaltered early development within the first year-post seizure onset. It is possible that infants having suffered complex FS do not present sequelae within this timeframe, or they are still too young for any possible sequelae to be detected by objective measures. These participants were studied at an age when cognitive capacities have yet to be differentiated, and can only be evaluated as such. At school-age, intellectual abilities are unaltered, as expected. However, these participants demonstrate weaknesses in particular cognitive domains, including executive functioning, and to a lesser extent, learning and memory abilities, relative to controls and the general population. These weaknesses worsen as a function of seizure duration. As such, our results indicate that children presenting with complex FS, including multiple and prolonged seizures without meeting criteria for FSE, show difficulties in specific cognitive capacities within the first six years of their life, at a time when cognitive functions begin to specialize in the developing brain.

Limitations of the current study must nevertheless be considered. The small sample sizes of both groups in both cohorts limit our statistical power and possibly mask effects that are

present but undetected, which of course require additional research and replication. Moreover, behavior/emotional outcome was assessed using parental questionnaires, which inherently limits our interpretation of the results, as previously discussed. In future, administering a parental stress questionnaire could help disentangle the nature of these results. In the school-age cohort, no children having suffered complex focal seizures could be recruited for the study, limiting our results to complex multiple and prolonged FS. Some studies (Wallace, 1996; Berg & Shinnar, 1996) have argued for a negative impact of focal and localized seizures on cognitive outcome, necessitating future research to include this subgroup of complex seizures in their studies.

In conclusion, our results suggest that development remains normal within the first year-post complex FS onset, although specific cognitive domains seem to be affected at school-age. The longer the seizure duration, the more significant are weaknesses related to executive functioning, learning and memory. Additional research is required to shed light on the heterogeneity of febrile seizures, as well as better understand the interplay between genetic and environmental factors and their impact on cognition. Follow-up regarding the impact of complex FS on cognition is necessary, beyond the developmental years and into adulthood, in understanding their long-term outcome.

REFERENCES

Achenbach T.M, Rescorla, L.A. Manual for the ASEBA Preschool forms and Profiles. 2000. Burlington, VT: University of Vermont Department of Psychiatry.

Achenbach, T.M., & Rescorla, L. A. Manual for the ASEBA School-Age Forms and Profiles. 2001. Burlington, VT: University of Vermont, Research Center for Children, Youth, and Families.

Anderson, S. Trajectories of brain development: point of vulnerability or window of opporunity? Neuroscience and Biobehavioral Review, 2013; 27, 3-18.

Baulac, S., Gourfinkel-An, I., Nabbout, R. et al. Fever, genes and epilepsy. Lancet Neurology 2004; 3: 421-430.

Bayley, N. Bayley scales of infant and toddler development - third edition. 2005. The Psychological Corporation, San Antonio, TX.

Berg, A., Shinnar., S. Complex Febrile Seizures. Epilepsia, 1996; 37, 126-133.

Blakesley, R. E., Mazumdar, S., Dew, M. A., Houck, P. R., Tang, G., Reynolds, C. F., 3rd, et al. Comparisons of methods for multiple hypothesis testing in neuropsychological research. Neuropsychology, 2009; 23(2), 255-264.

Brassen, S., Weber, W., Sommer, T. et al. Hippocampal-prefrontal encoding activation predicts whether words can be successfully recalled or only recognized. Behavioral Brain Research 2006, 171, 271-278.

Cendes, F., Andermann, F., Dubeau F., Gloor, P., Evans, A., Jones-Gotman, M. et al. Early childhood prolonged febrile convulsions, atrophy and sclerosis of mesial structures, and temporal lobe epilepsy: an MRI volumetric study. Neurology 1993; 43: 1083-1087.

Chang YC, Guo NW, Huang CC, Wang ST, Tsai JJ. Neurocognitive Attention and Behavior

Outcome of School‐Age Children with a History of Febrile Convulsions: A Population Study. Epilepsia 2000; 41: 412-420.

Chang, Y., Guo, N., Wang, S., Huang, C., Tsai , J. Working memory of school-aged children with a history of febrile convulsions: a population study. Neurology 2001; 57: 37-42.

Conners, C. K. Manual for the conners' parent rating scale-revised. 1997. Toronto, ON: MultiHealth Systems

Davis, K., Hermann, B., Dohan.F. Relationship of hippocampal sclerosis to duration and age at onset of epilepsy, and childhood febrile seizures in temporal lobectomy patients. Epilepsy Res 1996; 24: 119-126.

Delis, D. C., Kramer, J. H., Kaplan, E., & Ober, B. A. California Verbal Learning Test for Children. Manual. 1994. San Antonio, TX: Psychological Corporation

Ellenberg JH, Nelson KB. Febrile seizures and later intellectual performance. Archives of neurology 1978; 35: 17-21.

Hara H, Hara M, Fukuyama Y. Sustained attention in children with febrile convulsions. Brain Dev 1986; 8:557-8.

Hesdorffer, D., Caplan, R., Berg, A. Familial clustering of epilepsy and behavioral disorders: Evidence for a shared genetic basis. Epilepsia 2012; 53(2), 301-307.

Hesdorffer, D., Shinnar, S., Lax, D., Pellock, J., et al. Risk factors for subsequent febrile seizures in the FEBSTAT study. Epilepsia 2016; 57(7) 1042-1047.

Hilton, D., Jarrett, M., McDOal, K., Ollendick, T. Attenton problems as mediator of the relation between executive function and social problems in a child and adolescent outpatient sample. Journal of Abnormal Child Psychology 2017; 45(4), 777-788.

Hirtz DG. Cognitive outcome of febrile seizures. In: Baram T, Shinnar S, editors. Febrile seizures. San Diego: Academic Press; 2002, p. 53-62.

International League Against Epilepsy. Guidelines for epidemiologic studies on epilepsy. Epilepsia 1993;34:592–6.

Jay, T., Thierry, A., Wiklund L., Glowinski J. Excitatory amino acid pathway from the hippocampus to the prefrontal cortex. Contribution of AMPA receptors in hippocampo-prefrontal cortex transmission. European Journal of Neuroscience 1992; 4:1285–1295.

Kipp, K., Optiz, B., Becker, M, et al. Neural correlates of recognition memory in children with febrile seizures: evidence form functional magnetic resonance imaging. Frontiers in Human Neuroscience 2012; 6(17): 1-11.

Kipp, K., Mecklinger, A., Becker, M., et al. Infant Febrile Seizures: Changes in declarative memory as revealed by event-related potentials. Clinical Neurophysiology 2010; 121: 2007-2016

Korkman, M., Kirk, U., Kemp, S.L. NEPSY II. Clinical and interpretative manual. 2007. San Antonio, TX: Psychological Corporation.

Kolfen, W., Pehle, K., Konig, S. Is the long-term outcome of children following febrile

seizures favourable? Dev Med Child Neurology 1998; 40: 667-671.

Leaffer, E., Hinton, V., Hesdorffer, D. Longitudinal assessment of skill development in children with first febrile seizure. Epilepsy & Behavior 2013; 28, 83-87.

Leung, A. K., & Robson, W. L. Febrile convulsions: how dangerous are they? Postgraduate Medicine 1991; 89, 217- 224.

Lewis DV, Shinnar S, Hesdorffer DC, Bagiella E, Bello JA, Chan S, et al. Hippocampal sclerosis after febrile status epilepticus: The FEBSTAT study. Annals of Neurology 2014; 75: 178-185.

Lippe, S., et al. Altered EEG spectral activity and attentional behavioral deficits following prolonged febrile seizures: a pilot study. Epileptic Disord 2009; 11(1): p. 10-9.

Lucas, M., Lenck-Santini, P., Holmes, G., Scott, R. Impaired cognition in rats with cortical dysplasia: additional impact of early life seizures. Brain 2011; 134: 1684-1693.

Martinos, M., Yoong, M., Patil, S., Chin, R., Neville, B., Scott, R., de Hann, M. Recognition memory is impaired in children after prolonged febrile seizures. Brain 2012, 135: 3153-3164.

Martinos MM, Yoong M, Patil S, Chong WK, Mardari R, Chin RFM, et al. Early developmental outcomes in children following convulsive status epilepticus: A longitudinal study. Epilepsia 2013; 54: 1012-1019.

Miller, E., Cohen, J. An integrative theory of prefrontal cortex function. Annual Review Neuroscience 2001; 24:167–202.

Maytal, J., Shinnar., S. Febrile Status Epilepticus. Pediatrisc 1990; 86, 611-616.

Norgaard, M., Ehrenstein, V., Nielson, G., Rothman, K., Sorenden, H. Febrile seizures and cognitive function in young adult life: a prevalence study in Danish conscripts. Journal Pediatrics 2009; 155:404-409.

Patel, A. & Perry, S. Febrile Seizures: Evaluation and treatment. Journal of Clinical Outcomes Management 2017; 24(7), 325-334.

Petrides, M., Pandya, D. Association fiber pathways to the frontal cortex from the superior temporal region in the rhesus monkey. J. of Comparative Neurology 2004, 273(1), 52-66.

Provenzale JM, Barboriak DP, VanLandingham K, MacFall J, Delong D, Lewis DV. Hippocampal MRI signal hyperintensity after febrile status epilepticus is predictive of subsequent mesial temporal sclerosis. American Journal of Roentgenology 2008;190: 976-983.

Rhoades, B., Warren, H., Domitrovich, C., Green, M. Examining the link between preschool social-emotional competence and first grade academic achievement: The role of attention skills. Early Childhood Research Quarterly 2011; 26(2), 182-191.

Riggs, N., Jahromi, L., Razza, R., Dilworth-Bart, J., Mueller, U. Executive function and the promotion of social-emotional competence. Journal of Applied Developmental Psychology 2006; 27(4), 300-309.

Shinnar S. Febrile seizures. In: Swaiman K, Ashwal S, Ferriero D, Schor N, editors.

Swaiman's Pediatric Neurology. Fifth ed: Elsevier Saunders; 2012, p. 790-797.

Shinnar S. Febrile seizures and mesial temporal sclerosis. Epilepsy Currents 2003; 3: 115-118.

Shinnar S, Bello JA, Chan S, Hesdorffer DC, Lewis DV, MacFall J, et al. MRI abnormalities following febrile status epilepticus in children The FEBSTAT study. Neurology 2012; 79: 871-877.

Shinnar, S. & Glauser, T. Febrile Seizure. Journal of Child Neurology 2002; 17, s44-s52.

Steering Committee on Quality Improvement Management- Subcommittee on Febrile Seizures. Febrile Seizures: Clinical Practice Guideline for the Long- term Management of the Child With Simple Febrile Seizures. 2008; 121: 1281- 1286.

Stafstrom C. The incidence and prevalence of febrile seizures. In: Baram T, Shinnar S, editors. Febrile seizures. San Diego: Academic Press; 2002, p. 1- 25.

Thierry, A.M., et al., Hippocampo-prefrontal cortex pathway: anatomical and electrophysiological characteristics. Hippocampus 2000, 10(4): p. 411-9.

Tsai, M., Hung, K., Tsan, Y., Tao-Hsin, W. Long-term neurocognitive outcome and auditory event-related potentials after complex febrile seizures in children. Epilepsy & Behavior 2015; 47, 55-60.

Verity C, Butler N, Golding J. Febrile convulsions in a national cohort followed up from birth. I--Prevalence and recurrence in the first five years of life. BMJ 1985; 290: 1307-1310.

Verity CM, Greenwood R, Golding J. Long-term intellectual and behavioral outcomes of

children with febrile convulsions. New England Journal of Medicine 1998; 338: 1723-1728.

Visser, A., Jaddoe, V., Ghassabian, A., Schenk, J., Verhulst, F., Hofman, A., Tiemeier, H., Moll., H. Febrile seizures and behavioral and cognitive outcomes in preschool children: the Generation R Study. Developmental Medicine & Child Neurology 2012; p. 1006-1011.

Wallace, S. Febrile Seizures. Epilepsia 1996; 2(1), 28-33.

Wechsler, D. The Wechsler Preschool and Primary Scale of Intelligence, Third Edition (WPPSI-III). 2002. San Antonio, TX: The Psychological Corporation

Weiss, E., Masur, D., Shinnar, S., Hesdorffer, et al. Cognitive functioning one month and one year following febrile status epilepticus. Epilepsy & Behavior, 2016; 64; 283-288.

Wilmhurst, J., Gaillard, W., Vinayan, K., Tsuchida, T., Plouin, P., et al. Summary of recommendations for the management of infantile seizures: Task force report for the ILAE commission of Pediatrics. Epilepsia, 2015; 56(8): 1185-1197.

Ku, Y., Muo, C., Ku, C., Chen, C., Lee, W., Shen, E., Chang, Y., Kao, C. Risk of subsequent attention deficit-hyperactivity disorder in children with febrile seizures. Arch Dis Child 2013; 0:1-5

Table 1. Infant cohort sample descriptives for simple and complex FS groups

	Simple FS group n = 30 Mean (Std)	Complex FS group n = 35 Mean (Std)
Seizure type (% per group)		
Simple (n =30)	100%	
Multiple (n = 19)		54.2 %
Prolonged (n = 10)		28.5%
Focal (n = 6)		17.1%
Sex (%)		
Female (Simple n = 16; Complex n = 19)	53.3%	54.2%
Male (Simple n = 19; Complex n = 16)	46.6%	45.7%
Age at test (months)	17.05 (6.30)	20.29 (9.03)
Age at seizure onset (months)	15.23 (5.80)	16.39 (7.47)
Familial income ($ CAN)	67 230.76 (23 428.71)	75 375.00 (24 880.03)
Mother's education (years)	15.07 (3.6)	15.91 (2.1)
Father's education (years)	15.23 (5.80)	16.39 (7.47)
Time between last seizure and test (months)	1.7 (1.6)	3.03 (4.11)

Table 2. Infant cohort developmental scores on the Bayley-III for simple and complex FS groups

	Simple FS group n = 30 Mean (Std)	Complex FS group n = 35 Mean (Std)	*F*	*p*
Cognition	10.66 (1.7)	10.42 (2.42)	0.20	0.65
Receptive communication	9.63 (2.14)	10.11 (3.30)	0.46	0.49
Expressive communication	10.03 (1.9)	9.48 (2.68)	0.86	0.35
Fine motor	11.03 (2.60)	10.88 (2.70)	0.05	0.82
Gross motor	9.8 (2.56)	9.9 (3.39)	0.01	0.89

Note. Results are presented in scaled scores for the five scales, and in standard scores for the three composite scores.

Table 3. School-age cohort sample descriptives for simple, multiple and prolonged FS groups

	Simple FS group n = 19 Mean (Std)	Complex Multiple FS group n = 11 Mean (Std)	Complex Prolonged FS group n = 10 Mean (Std)
Sex (%)			
Female	57.8%	18.1%	70%
Male	42.1%	81.8%	30%
Age at test (years)	6.00 (0.44)	6.00 (0.32)	6.04 (0.23)
Age at seizure onset (years)	1.33 (0.33)	1.04 (0.46)	1.27 (0.62)
Familial income ($ CAN)	79 368.4 (26 179.3)	90 454.5 (42 629.5)	77 500.0 (23 717.1)
Mother's education (years)	16.5 (2.0)	15.0 (2.0)	15.0 (2.6)
Father's education (years)	15.2 (2.6)	14.8 (2.9)	15.3 (2.4)

Table 4. School-age cohort neuropsychological composite scores for simple, multiple and prolonged FS groups

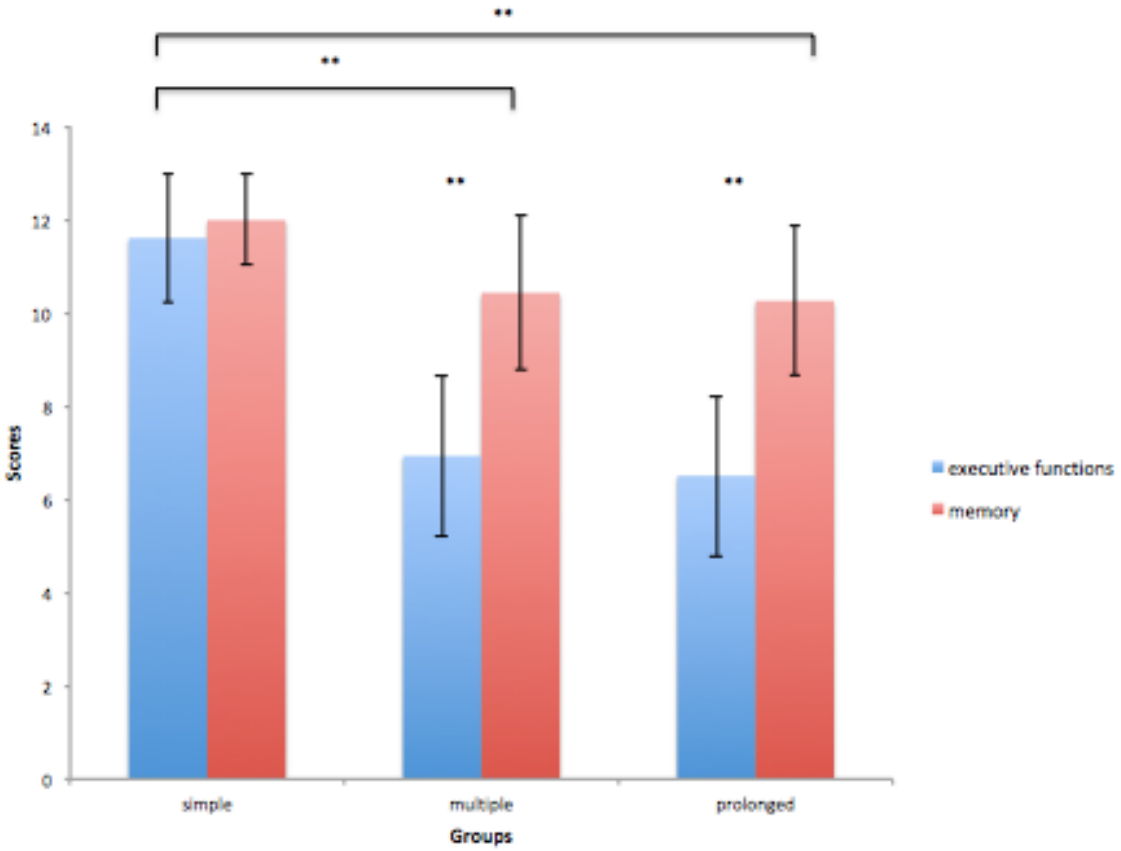
	Simple FS group n = 19 Mean (Std)	Complex Multiple FS group n = 11 Mean (Std)	Complex Prolonged FS group n = 8 Mean (Std)
WPPSI-III			
Global IQ	106.05 (15.12)	94.56 (11.36)	106.25 (16.47)
Cognitive Domain			
Executive Function	11.60 (1.37)	6.92 (1.72) **	6.5 (1.72) **
Memory	11.98 (0.97)	10.42 (1.64) *	10.25 (1.59) *

Note. Results for the WPPSI-III are presented in standard scores. Results of the cognitive domains are presented in weighted scaled scores.

** $p < 0.01$

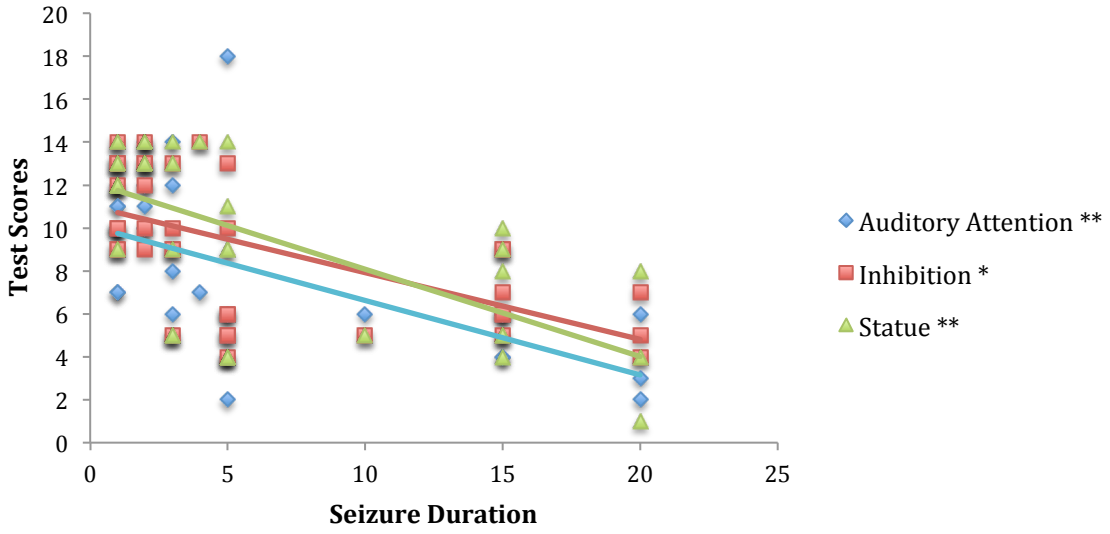
* $p < 0.03$

Figure 1. School-Age group differences according to cognitive domain



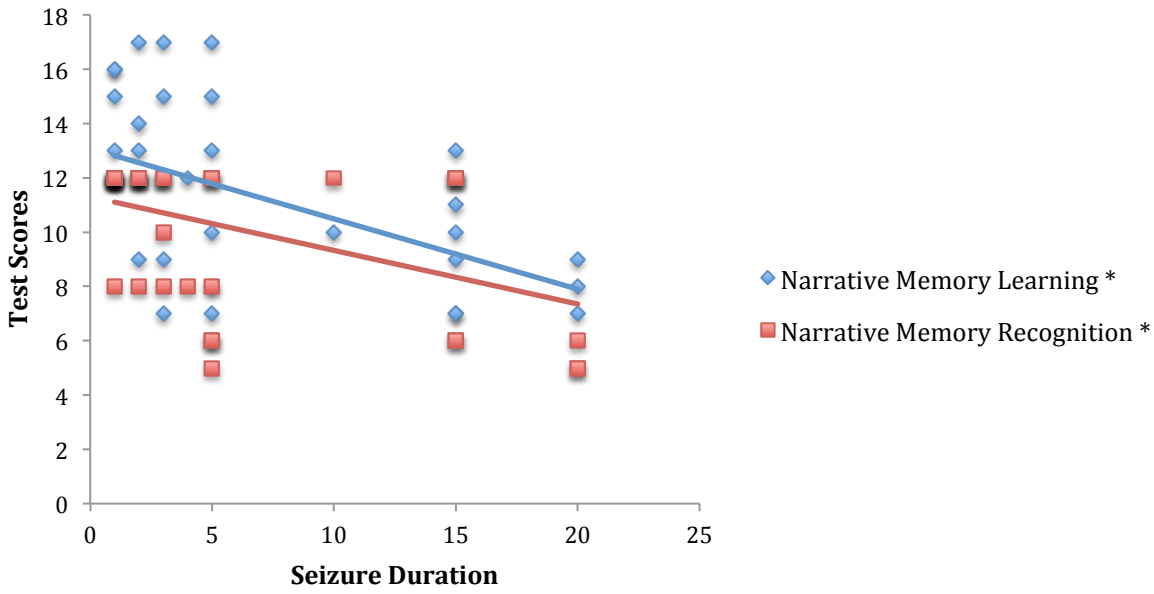
Note. Scores are presented in weighted scaled scores
*** p < 0.01*
** p < 0.03*

Figure 2. Correlations between executive functioning measures and seizure duration



Note. Results of test scores are presented in scaled scores with a mean of 10 and a standard deviation of 3; the higher the score, the better the performance.
*** p < 0.0001*
** p < 0.01*

Figure 3. Correlations between learning and memory measures and seizure duration



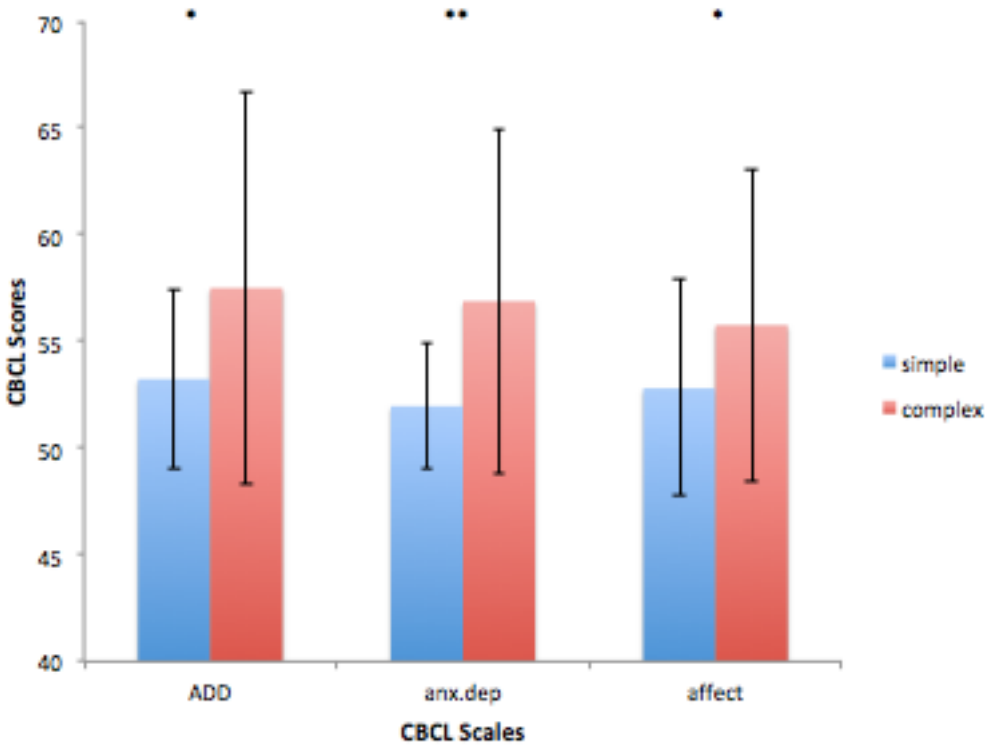
Note. Results of test scores are presented in scaled scores with a mean of 10 and a standard deviation of 3; the higher the score, the better the performance.
*** p < 0.0001*
** p < 0.01*

Table 5. Behavior/ emotion scores on the CBCL for simple and complex FS groups across both cohorts

	Simple FS group n = 30 Mean (Std)	Complex FS group n = 34 Mean (Std)	*F*	*p*
Affective problems	52.80 (5.06)	55.76 (7.31)	2.15	0.14
Anxiety problems	53.13 (4.86)	57.20 (8.71)	3.45	0.06
Attention deficit/ hyperactivity problems	53.23 (4.24)	57.20 (9.17)	4.81	0.03
Oppositional defiant problems	53.50 (5.96)	56.82 (7.44)	3.50	0.06
Anxious/ depressed	51.96 (2.95)	56.88 (8.07)	8.08	0.006
Somatic Complaints	52.76 (5.46)	54.20 (6.94)	0.44	0.51
Withdrawn	53.76 (4.95)	54.20 (5.86)	0.01	0.90
Attention problems	53.33 (6.04)	57.00 (7.02)	4.44	0.03
Aggressive behavior	53.33 (6.79)	56.50 (8.25)	1.80	0.18

Note. Results are presented as t-scores; the higher the score the more problematic are the behaviors

Figure 4. Significant CBCL group differences across both cohorts



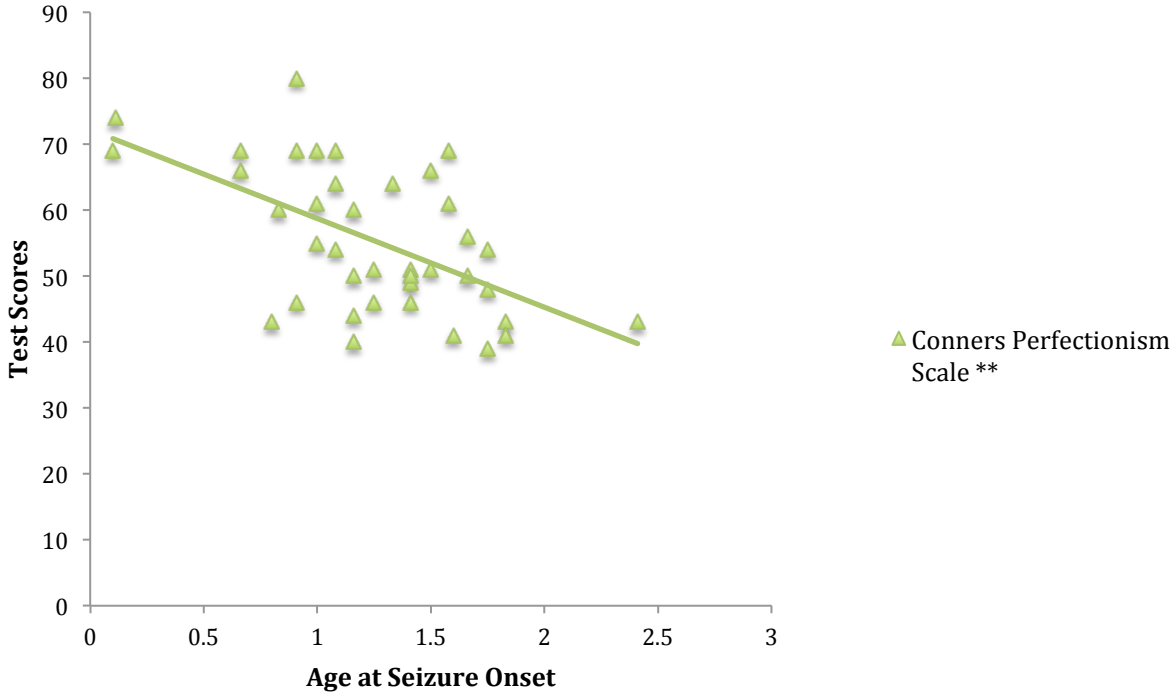
Note. Scores are presented in T-scores; the higher the value, the worse the performance.
** $p < 0.01$
* $p < 0.05$

Table 6. School-age cohort behavior/emotion scores on the Conners for simple, multiple and prolonged FS groups

	Simple FS group n = 19 Mean (Std)	Complex Multiple FS group n = 11 Mean (Std)	Complex Prolonged FS group n = 8 Mean (Std)
Conners			
Hyperactivity	50.9 (6.7)	63.2 (12.9)*	59.3 (11.3)
Oppositional	50.1 (9.2)	56.6 (13.0)	54.4 (9.1)
Cognitive problems	49.9 (6.5)	59.5 (14.7)	48.4 (10.5)
Shy/Anxious	48.6 (6.9)	56.6 (9.3)	53.3 (12.9)
Perfectionism	52.9 (8.6)	55.1 (12.5)	60.2 (12.5)
Psychosomatic	50.2 (4.8)	54.4 (13.5)	51.4 (5.4)

Note. Results are presented in t-scores; the higher the score, the worse the performance.
** $p < 0.0001$
* $p < 0.01$

Figure 5. Correlation between Conners Perfectionism Scale and age at seizure onset



Note. Results of test scores are presented in t-scores; the higher the score, the worse the performance.
*** p < 0.0001*
** p < 0.01*

GENERAL DISCUSSION

Epileptic syndromes throughout the lifespan have consistently been associated with poor cognitive outcome, typically in relation to etiology, age at onset, seizure type and severity, seizure duration and treatment, significantly impacting function and quality of life (Motamedi, 2003; Moorthy et al., 2018). In considering the pediatric population more specifically, epileptic encephalopathies have similarly been linked to progressive cognitive dysfunction in the developing brain (Dulac, 2001; Khan & Baradie, 2012). Evidence related to the impact of seizure events occurring in isolation, without defining or being part of any broader syndrome has however not been as convergent.

Following early-life SE, evidence supports significant physiological alterations, which have further been linked to persisting cognitive residua related to altered development, global intelligence, learning capacities and executive function, particularly as they occur in the developing brain (Sheppard & Lippé, 2012). Febrile seizures, although less severe than SE, are the most common form of childhood seizure, for which cognitive outcome remains unclear (Shinnar & Glauser, 2002). Although physiological alterations, particularly of the hippocampus, have been consistently shown in the most severe forms of FS, and a lesser extent in other forms of complex FS, studies investigating cognitive and behavioral outcome to date have examined cognitive capacities in isolation using measures that lacked objectivity, specificity and standardization, and generally restricted to the most severe forms of FS.

The objective of the current clinical investigation was to study development and cognition following an initial complex FS from onset to school-age, in the context of known risk factors

for poor outcome, including all types of complex features. More specifically, we aimed to study the impact of an initial complex FS on development and behavior within the first year-post onset using comprehensive standardized measures, and recruiting a clinical sample that included an exceptionally wide range of complex FS features (i.e., prolonged between 15 and 30 minutes, recurrent and focal). Furthermore, we aimed to examine cognitive development in a cohort of children old enough for cognitive functions to be sufficiently differentiated (i.e., school-age) to allow specific, objective and standardized assessment of the impact of different types of complex features on specific functions, particularly related to learning/memory and executive function.

FINDINGS

In investigating the impact of suffering a complex FS on development within the first year post-onset, our results revealed no differences in cognitive, motor and language development between infants having suffered complex FS and simple FS controls. Moreover, infants of both groups scored within average ranges as compared to the general population. Although these results are consistent with previous findings showing developmental scores within average ranges at baseline and one year-post onset following FSE, previous results had further demonstrated a slight gap in developmental trajectories between infants having suffered FSE and controls within this timeframe (Weiss et al., 2016; Martinos et al., 2012). In considering risk factors, seizure duration and age at seizure onset were not associated with outcome. Overall, our first hypothesis could not be confirmed. Children having suffered complex FS did

not show weaker development, and longer seizure durations and younger ages of onset did not impact outcome.

At school-age however, several significant group differences were observed. Although our results revealed no impact of complex FS on global intelligence, consistent with previous findings (Ellenberg & Nelson, 1978; Verity et al., 1998; Hirtz, 2002), significant differences are noted in specific cognitive abilities. In particular, children having suffered complex prolonged and complex multiple FS demonstrated significantly weaker executive capacities, and to a lesser extent, weaker learning and memory abilities, as compared to simple FS controls. Moreover, these cognitive challenges were associated with longer seizure durations. As such, our second hypothesis was confirmed.

Regarding behavior and emotions, parents of children having suffered complex FS showed significantly more concerns related to attention problems, anxious/depressive symptomology and affective problems, consistently from onset to school-age. At school-age more specifically, parents demonstrated significant concern on a hyperactivity scale. These challenges were however unaffected by seizure characteristics. In contrast, earlier ages at onset were associated with higher perfectionist traits. Given the subjective nature of the behavioral measures however, confounding parental stress and concern could not be ruled out.

Taken together, results of this study can begin to shed light on understanding the long-term impacts of early-life FS on cognitive and emotional development throughout infancy and into childhood.

Cognitive development

In light of the current results, we can begin to understand cognitive development beyond the first year post-FS onset and into childhood. In considering complex FS features, namely focal, multiple or prolonged (i.e., between 15 and 30 minutes of duration), we propose that complex FS do not alter development or behavior within the first year post-onset. Given that previous studies have found mild early gaps in developmental trajectories in the first year following FSE onset, longer seizure durations (i.e., between 70 and 90 minutes) may play the key factor in severity and impact on early development (Weiss et al. 2016; Martinos et al., 2012; 2013).

At school-age, a time when cognitive capacities have differentiated sufficiently to allow their specific and objective assessment, children having suffered complex FS (i.e., prolonged between 15 and 30 minutes and multiple FS) demonstrate significant executive difficulties as compared to controls and the general population. Specifically, challenges in selective and sustained attention, inhibition, idea generation and hyperactivity are observed, to the extent that performances are within clinical ranges. These results can be corroborated by evidence demonstrating increased occurrence of behavior disorders in children having suffered FS, including ADHD, characterized by age-inappropriate attention, hyperactivity and impulsive behavior (Hara et al., 1986; Chang et al., 2001; Hesdorffer et al., 2012; Ku et al., 2013). More specifically, children with a history of FS have been shown to have a 20% to 30% increased risk of ADHD compared with children without FS (Bertelsen, 2016), and this disorder has been shown to occur in about 30% of children with epilepsy (Besag, 2016). In broader terms, executive dysfunctions have been shown to be affected in a multitude of neurodevelopmental

disorders beyond ADHD, including conduct disorder, autism and Tourette's syndrome (Ozonoff et al., 1999; Shanmugan, 2016), suggesting either specific commonalities between conditions leading to their impact on executive functions (e.g., common genetic factors, common environmental risk factors), or that the mechanisms involved in executive functioning are particularly sensitive to features of these developmental disorders.

Our results further revealed that children having suffered complex FS demonstrated weaker performances on learning and memory tasks, albeit to a lesser extent than executive functions, as compared to children having suffered simple FS. These results are consistent with previous findings demonstrating a negative impact of prolonged FS or febrile status epilepticus on memory functions, including recognition memory, which was further associated with hippocampal anomalies (Martinos et al., 2012; Weiss et al., 2016). Given that performances on learning and memory tasks were also worse as seizure duration increased, it is possible that prolonged FS (i.e., between 15 and 30 minutes duration) represent similar impacts on cognition as FSE, just to a lesser degree on the spectrum of severity of outcome.

Taken together, although early development is unaffected within the first year-onset, and global intelligence is unaltered in school-age children, these children demonstrate challenges related to specific cognitive capacities, including executive functioning and memory. These difficulties are observed at an age when cognitive capacities have differentiated sufficiently to be assessed. Even though there seems to be an evolution of cognitive sequelae over time and development as the brain matures, age at onset was not associated with outcome. In fact, seizure duration seemed to be the main influence on cognitive outcome, consistent with

previous evidence related to FSE, even though children having suffered multiple complex FS demonstrated similar difficulties, albeit to a slightly lesser qualitative extent, overall suggesting that complex features that are not as severe as FSE may still demonstrate cognitive sequelae at school-age. Moreover, cognitive challenges were demonstrated beyond hippocampus-dependent cognitive functions, namely learning and memory, and seemed to significantly extend to the executive functions in both prolonged and multiple FS.

Emotional / behavioral development

From onset to school-age, our results indicate behavioral/emotional challenges in children having suffered complex FS, including attention problems, anxious/depressed symptomology and affective problems, as observed by caregivers. At school-age, behavioral challenges are highlighted on a scale of hyperactivity for these children. Moreover, perfectionist traits were observed to increase with younger ages of onset. In contrast to cognitive measures, emotional challenges were unaffected by seizure duration. These results are consistent with previous evidence demonstrating that recurrent seizures significantly predicted internal problems relatively early in the course of a seizure condition (Austin, 2002).

Although associations are observed between FS and emotional/behavioral challenges, the direction and interpretation of these associations can be debated. It can be argued for example, that both seizures and emotional challenges are subserved by similar underlying physiological anomalies, or the seizure per se may impact physiology which impacts emotion regulation, or further, perhaps disrupted emotions are a negative psychological response to the seizure. In exploring psychiatric conditions comorbid to FS and seizure disorders, evidence has shown

that children with a history of FS have a 44% increased risk of developing a psychiatric condition, particularly schizophrenia (Vestergaard, et al., 2005). Moreover, children suffering from epilepsy have demonstrated a 5.5-fold increased risk of developing psychosis, and 8.5-fold increased risk of developing schizophrenia (Clarke, et al., 2012). Other psychiatric comorbidities following seizure disorders include anxiety, depression, bipolar disorder and sleep disorders (Clarke et al., 2012; Motamedi, 2003). Nakahara et al. (2018) suggested a common hippocampal pathophysiology in TLE and psychiatric disorders, although it remained unclear whether the pathophysiology linked to TLE was also linked to the psychiatric disorders, or if the disorders occurred subsequent to TLE. Taken together, there seems to be an underlying pathophysiology between seizures and emotional difficulties, which however does not rule out the possibility of negative psychological reaction to seizures, particularly in considering our results, such that increased internal difficulties could also, to a certain extent, reflect an emotional reaction to early-life seizure occurrences.

NEURODEVELOPMENTAL CONTEXT

Febrile seizures occur at an age when the brain is in rapid maturation, and implementation of functional specialization is at its peak rate of change. In considering the impact of an early life insult to the brain on cerebral and cognitive development, the Vulnerability theory posits that owing to the lack of functional specialization in the developing brain, it will attempt to recover endangered functions from a damaged structure by aberrantly creating faulty connections, therefore hindering the healthy development of future structures, and further, the cognitive abilities subserved by these structures. With regards to seizure disorders in early life, it is

argued that abnormal electrical activity will compete with normal brain activity for neural resources (Pavlidou, 2007). If abnormal activity occurs at critical stage of cerebral development, aberrant neuronal connections may be formed and normal brain functions may fail to develop.

Our results demonstrate significantly impacted executive functions, and to a lesser extent, learning and memory in school-age children having suffered complex FS, although infants assessed within the first year-post onset demonstrated normal and unaltered development, suggesting that the impact of early-life seizures could only be detected later in life. Although executive functions are known to develop exponentially between the ages of 7 and 10 and continue developing into early adulthood, Anderson et al. (2010) demonstrated that brain insults occurring prior to the age of three recorded greater global and severe executive functioning deficits in later life as compared to children of older age. These results support our findings, which in turn bring support to the Vulnerability theory. Moreover, our absence of impact of age at seizure onset on cognition could therefore likely be explained by the fact that all our participants had seizure onsets prior to three years of age. Seizure duration was found to be the main influence on cognitive outcome, such that the longer the seizure, the more the developing structures are submitted to the potentially damaging effects of the seizure event, especially for structures that have been shown to be particularly vulnerable, including the hippocampus (Anderson, 2003). Indeed, transient and long-term hippocampal damage has consistently been shown following FSE, further associated with cognitive challenges related to learning and memory, detected even within the first year post-onset (Shinnar et al, 2012; Weiss et al 2016). Our results also show learning and memory challenges following complex

FS, specifically related to prolonged seizures (i.e., between 15 and 30 minutes), although to a lesser degree of impairment than observed in previous FSE studies, and only detected later in life (i.e., school-age), which could indicate similar structural involvement (i.e., hippocampus), but less severe degree of physiological alterations.

CEREBRAL STRUCTURES INVOLVED IN FS

The hippocampus has been the principle structure studied to date through animal models and different types of imaging techniques. As previously mentioned, converging evidence suggests its long-term alterations following events of FSE, further associated to challenges in the development of hippocampus-dependent functions. In the context of our results, which show significant cognitive challenges beyond hippocampus-dependent functions in school-age children, including impacted executive functions, it is argued that faulty hippocampal development following FS may subsequently alter the development of other structures.

Specifically, it is possible that early damage to the hippocampus may cause faulty related neuronal networks, including the cortico-hippocampal network. From a structural perspective, this network encompasses direct and monosynaptic connections between the hippocampus and frontal/prefrontal areas, which have further been shown to be synchronized by theta-rhythm oscillations (Petrides & Pandya, 2004; Benchenane, 2010). Functionally, the cortico-hippocampal network has been shown to be a key player in learning and memory capacities by binding information into a coherent memory trace, as well as attention and inhibitory response control (Wall & Messier, 2001; Eichenbaum, 2000; Brassen, 2006; Bast et al., 2017). In

considering the impact of seizures on this network, patients suffering from TLE have demonstrated widespread disturbances in white matter tracts in the temporal lobe and extratemporal regions, which have been linked to cognitive impairment (Riley et al, 2010). Moreover, the flexibility of the cortio-hippocampal network in particular has been shown to be altered in TLE patients, such that a reduced task-dependent reshaping of network interactions has been observed (Tailby et al., 2018), and impairments in brain theta oscillations in the frontal area in TLE patients have been argued to subserve poor executive control of behavior (Li et al., 2018). In considering FS, animal models have begun to demonstrate associations between cognitive impairments following experimentally-induced FS and network dysfunctions involving the hippocampus and prefrontal cortex (Dubé et al., 2009). Taken together, the importance of network dysfunction (i.e., beyond the structure-function relationships of cognition in epilepsy) in understanding the cognitive deficits observed in seizure disorders can be argued. Of further note, the cortico-hippocampal network has consistently been shown to be involved in psychiatric disorders, including anxiety and schizophrenia, which could in turn also indicate common pathophysiology between seizure and psychiatric disorders (Kupferschmidt & Gordon, 2018; Ploghause et al., 2001). Of course, the involvement of the cortico-hippocampal network in cognitive dysfunction following FS is speculative at this point in time, although it may be an important research consideration, which could eventually bring greater understanding to the impact of FS on cerebral and cognitive development.

HETEROGENEITY OF FEBRILE SEIZURES

A key factor in the divergent evidence related to outcome following FS lies in the heterogeneity of their presentation. With regards to their impact on physiology, complex features outside of FSE have been largely understudied, although the few studies performed also suggest a negative impact of focal and recurrent features on physiology to arguably different degrees of severity, which overall resemble controversies in the evidence related to cognitive development following FS (Hesdorffer et al., 2008; Yoong et al, 2013). Our current studies were designed to include all complex FS types (i.e., prolonged between 15 and 30 minutes, focal and recurrent seizures) in attempting to bring some understanding to their possible differential impacts on cognitive development. In school-age children, those having suffered both multiple and prolonged seizures demonstrated executive, and to a lesser extent, learning and memory challenges, although these challenges were associated with seizure duration. As such, is possible that either both types of complex features are on a common spectrum where prolonged FS seem to have greater impact on cognitive development, or it could be argued that seizures with different complex features could be considered separate entities altogether. Additional research on multiple and focal FS, from physiological and functional perspectives are required to better disentangle this debate.

From a broader vantage point, the understanding of how some children will develop FS, while other will not, in the context of a similar systemic illness and fever presentation, and further, how some children presenting with FS go on to develop full-blown encephalopathies while others do not, is still unclear to researchers. The heterogeneity in FS presentation seems to be underlined by multifactorial etiologies and interactions between genetic predispositions and environmental factors.

CAUSE VERSUS CONSEQUENCE

Research to date argues for multifactorial etiologies in FS, given their heterogeneous nature. Long-standing "chicken or the egg" debates have posited that either FS occur in immature brains that are predisposed for seizure activity, or FS occur in otherwise healthy brains that in turn cause transient and long-term damage, further complicated by a an interweaving web of possible interactions between genetic and environmental risk factors. Evidence to date has inconsistently shown direct links between seizure characteristics and outcome, suggesting that outcome is not entirely explained by the seizure event per se (Weiss et al, 2016; Martinos et al, 2012; 2013). Nevertheless, studies have also demonstrated some associations between seizure features and cognitive outcome (Chang et al., 2000; 2001), consistent with our findings indicating a link between seizure duration and cognitive outcome, as well as between age at seizure onset and emotional outcome, suggesting that the seizure event per se, at least in part, influences, or possibly exacerbates outcome. Taken together, it is highly unlikely that a FS event itself causes cerebral damage leading to poor cognitive outcome. Rather, multifactorial etiologies and risk factors seem to contribute to an initial FS, and multifactorial modulators seem to impact the possibility of seizure recurrence and cognitive outcome, even though a clear portrait of influencing factors, the context in which these factors are expressed, and direction of their relationship to outcome has yet to be established.

Moreover, in examining the phenotype of cognitive and behavioral outcome more specifically, other cause/consequences debates can be argued for the likely bidirectional relationship

between cognitive and emotional outcome following FS. Indeed, several studies have demonstrated the role of executive functioning in behavioral and emotional dysregulation, including their role in social behavior and disorders such as anxiety, depression, obsessive-compulsive disorder, panic disorder and eating disorders (Rao et al., 2013; Shanmugan, 2016). Conversely, emotional dysregulation can also negatively impact the use of cognitive functions. Although cognitive challenges following FS seem to be, at least in part, organic in nature (i.e., related to physiological alterations), and although the nature of emotional challenges following FS has been largely understudied and remains unknown, it is possible that a bidirectional exacerbation of cognitive and emotional challenges exists.

IMPLICATIONS

For research

Our studies were part of few that have investigated and compared different types of complex FS features, which have revealed the seemingly differential impact of seizure duration on cognitive outcome, and impact of recurrence on social problems in school-age children. Moreover, to our knowledge, our study of cognitive outcome in school-age children was the first to objectively assess and demonstrate executive function difficulties in this population. These findings can shed light on cognitive processes that are impacted following FS, beyond hippocampus-dependent functions, and further, possible emotional difficulties following the seizure event, that can open new research avenues, particularly in neuroimaging.

For clinicians

The current study could begin to establish a neuropsychological phenotype for children having suffered complex FS. As such, it has been established that these children demonstrate unaltered development in infancy, and unaltered global intelligence at school-age. Nevertheless, specific cognitive functions seem to be affected, including executive functioning, that is, attention (selective and sustained), inhibition, idea generation and hyperactivity, which are generally characterized by performances in low average ranges for children having suffered multiple and prolonged FS. Learning and memory challenges are also noted as a function of seizure duration, although to lesser extent and characterized by performances nevertheless remaining within average ranges. Given our results, behavioral and emotional challenges, that is, external (e.g., attention problems, hyperactivity) and internal problems (e.g., anxiety, depression, affective problems, perfectionism) in particular could be expected from children having suffered complex FS.

Of important note, although differences are seen at the group level, individual differences are many, particularly in the context of the heterogeneity of FS. As such, a child presenting with a complex FS will not necessarily demonstrate these observed challenges in later life. Conversely, if a child's developmental trajectories are normal following FS onset, the later development of their specific cognitive functions are not necessarily spared. Extensive review of medical, developmental and family history is necessary, and can orient clinicians to risk factors and modulators specific to the child, in trying to piece together their unique individual puzzle. Moreover, it is our hope that the current results can help orient intervention for these children. For example, if a child is observed to begin to present behavioral challenges within the first year post-onset, early executive interventions may help prevent exacerbations of

challenges in later life. Early intervention with parents of these children is also warranted, including education related to FS.

Parental concern

Of importance, and often omitted, are parental reactions to their child's FS occurrence, and how their reactions may in turn affect their child's outcome. In a study by Balslev (1991) on parental reactions to their child's first FS occurrence, results indicated that 60% of parents slept restlessly, 13% watched their child at night, and 29% demonstrated dyspeptic symptoms, even one year after the occurrence. Moreover, perinatal maternal emotional symptoms have been linked to earlier ages of FS onset (Thebault-Dagher et al. 2017). Interestingly though, results of the large prospective multicenter FEBSTAT study on the impact of FS revealed minimal parental stress at baseline and one year-post FSE, and therefore was not found to impact questionnaire completion (Shinnar et al., 2017). Nevertheless, education pertaining to FS should be provided to parents.

LIMITATIONS

Several limitations of our studies need to be considered in the interpretation and implications of our findings. Most notably, sample sizes in both our studies were small, which limits our statistical power and possibly masks effects that are present but undetected. Nevertheless, the significant results obtained are strong, particularly those obtained in the school-age cohort of children, and likely indicate persistent cognitive challenges following FS. Moreover, although participants presenting different types of complex FS were admissible in both studies, our

cases presented only one complex feature, even though about one third of children presenting with complex FS have one or more complex characteristics (Patel et al., 2015). As such, our results do not account for children presenting more than one complex feature. Moreover, no children with complex focal FS could unfortunately be recruited in our school-age cohort, and as such, our results similarly do not account for children having suffered focal FS. In addition, given that only about 33% of parents of eligible children agreed to participate in our first study and about 17% in our second study, a possible selection bias cannot be ruled out, even though proportions of complex FS features were similar to that of the complex FS population (Patel et al., 2017). In considering these limitations, our results may not be generalizable to the FS population at large, but rather to a subgroup of this vast heterogeneous population. Lastly, given the transversal nature of our overall study design, children assessed at infancy were not the same as those assessed at school-age, forgoing intra-subject analyses and longitudinal investigation of development over time. Overall, our results necessitate replication in order to promote generalizability, and future research is required to better understand the outcomes following FS.

FUTURE DIRECTIONS

The current findings can nevertheless shed light on cognitive processes that are impacted following FS, beyond hippocampus-dependent functions, and further, possible emotional difficulties following the seizure event, which in turn can open new research avenues, particularly in neuroimaging. More specifically, neuroimaging studies could begin to step outside the specificity of hippocampal analyses, and investigate other structures likely

involved in the physiology underlying FS, perhaps using different types of whole-brain analyses to help direct and orient to other cerebral areas that may be involved in FS. Moreover, connectivity analyses could shed light on the possibility of network dysfunctions, beyond the structure-function relationships known for cognition. In particular, such analyses could be performed in investigating the cortico-hippocampal network, in bringing insight into it's possible impact on cognitive development, and development of executive function following FS in particular. Furthermore, imaging studies related to the physiology of emotional challenges following FS could shed light on debates related to etiology of emotional struggles, and how their presentation interacts with cognitive outcome.

With regards to future directions in cognitive development following FS, complex features other than FSE are required to be studied, including focal and multiple seizures, and the combined presentation of more than one complex feature, in understanding their possible differential impact on outcome. Moreover, longitudinal studies would allow a more direct assessment of the evolution of cognitive development over time by allowing intra-subject analyses relating seizure characteristics, risk factors and outcomes in individual participants over time, and perhaps extended into adolescence, when brain maturity reaches a different level. Prospective studies, although much more complex, would allow for better understanding of the interplay between genetic and environmental factors, and the FS community is looking forward to gaining insights from the large prospective multicenter study (FEBSTAT) investigating the long-term outcomes following FSE.

CONCLUSION

In conclusion, although FS are considered a less severe form of childhood seizure, they are the most common. The present findings help bring light to the cognitive and behavioral sequelae following early-life complex FS. Although children having suffered complex FS do not show altered development within the first year post-onset, significant cognitive challenges are noted later in life, namely at school-age. In particular, difficulties in specific cognitive capacities, namely executive functioning and learning/memory, are observed in relation to seizure duration. Moreover, emotional and behavioral challenges are apparent in children having suffered complex FS, and can be related to younger ages of onset. Overall, our results indicate that multiple and prolonged (i.e., between 15 and 30 minutes of duration) FS are severe enough to demonstrate these cognitive and emotional sequelae, which are overall less severe than those observed following SE, and further, those observed in the broader spectrum of epileptic encephalopathies and epilepsy. Replication is however required in promoting the generalizability of our findings, and future research in neuroimaging and assessments beyond the childhood years could further expand our understanding of the heterogeneous nature of FS and their outcome.

REFERENCES - INTRODUCTION & DISCUSSION

Abou-Khalil B. (2010) The relationship between febrile seizures and epilepsy. *Epilepsia, 51;* 40–42

Abou-Khalil B, Krei L, Lazenby B, Harris PA, Haines JL, Hedera P (2007) Familial genetic predisposition, epilepsy localization and antecedent febrile seizures. *Epilepsy Res, 73*; 104–110

Aicardi, J., Chevrie, J. (1970) Convulsive status Epilepticus in Infants and Children a Study of 239 Cases. *Epilepsia, 11;* 187-197.

Aldenkamp, A. (2006). Cognitive impairment in epilepsy: State of affairs and clinical relevance. *Seizure, 15*; 219-220.

Andersen, S. (2003). Trajectories of brain development: point of vulnerability or window of opporunity? *Neuroscience and Biobehavioral Review*, *27*, 3-18.

Anderson, S., Classey, J., Conde, F., Lund, J., Lewis, D. (1995) Synchronous development of pyramidal neuron dendritic spines and parvalbumine-immunoreactive chandelier neuron axon terminals in layer III of monkey prefrontal cortex. *Neuroscience, 67*; 7–22

Anderson, V., & Moore, C. (1995). Age at injury as a predictor of outcome following pediatric head injury: A longitudinal perspective. *Child Neuropsychology, 1*(3), 187-202

Anderson, V., Bond, L., Catroppa, C., Grimwood, K., Keir, E, Nolan, T. (1997) Childhood bacterial meningitis: Impact of age at illness and acute medial complication on long term outcome. *J International Neuropsychological Society* 3, 147-158

Anderson, V., Spencer-Smith, M, Coleman, L. et al. (2010) Children's executive functions: Are they poorer after very early brain insult. *Neuropsychologia, 48*(7); 2041-2050.

Anderson, V. (2001) Assessing executive functioning in children: biological, psychological, and developmental considerations. *Pediatric Rehabilitation, 4*(3); 119-136.

Annegers, F., Hauser, A., Shirts, S., Kurland, L. (1987) Factors prognostic of unprovoked seizures after febrile convulsions. *New England Journal of Medicine, 316;* 493–8

Audenaert D, Van Broeckhoven C, De Jonghe P, et al. (2006) Genes and loci involved in febrile seizures and related epilepsy syndromes. *Hum Mut, 27*; 391-401

Austin, J., Dunn, D., Caffrey, H., Perkins, S., et al. (2002). Recurrent seizures and behavior problems in children with first recognized seizures: A prospective study. *Epilepsia, 43*(12); 1564-1573.

Balslev, T. (1991). Parental reactions to a child's first febrile convulsion: A follow-up investigation. *Acta Paediatrica, 80*(4), 466-469

Barr, W., Ashtari, M., Schaul, N. (1997). Bilateral reductions in hippocampal volume in adults with epilepsy and a history of febrile seizures. *Journal of Neurology, Neurosurgery and Psychiatry*, *63*, 461-467.

Baumann RJ, Duffner PK. Treatment of children with simple febrile seizures: the AAP practice parameter. American Academy of Pediatrics. *Pediatr Neurol 2000*, 23; 11–7

Baumer, J. (2004) Evidence based guideline for post-seizure management in children presenting acutely to secondary care. *Archives Dis Child, 89*(3), 278-280.

Bell, M. & Fox, N. (1992) The relations between frontal brain electrical activity and cognitive development during infancy. *Child Development, 63*; 1142-1163

Benchenane, K., et al., (2010). Coherent theta oscillations and reorganization of spike timing in the hippocampal- prefrontal network upon learning. *Neuron, 66*(6); 921-36.

Berg, A., & Shinnar., S. (1996) Complex Febrile Seizures. *Epilepsia, 37*; 126-133.

Berg, A, Shinnar, S, Darefsky, A, et al. (1997) Predictors of recurrent febrile seizures. A prospective cohort study. *Arch Pediatr Adolesc Med, 151*; 371-8

Berg T, Shinnar S, Levy R, Testa M. (1999) Childhood-onset epilepsy with and without preceding febrile seizures. *Neurology, 53*; 1742-8.

Bertelsen, E., Larsen, J., Petersen, L. et al. (2016) Childhood epilepsy, febrile seizures, and subsequent risk of ADHD. *Padiatrics, 138* (2); 1-11.

Besag, F., Gobbi, G., Caplan, R. et al. (2016). Psychiatric and behavioural disorders in children with epilepsy (ILAE task force report): Epilepsy and ADHD. *Epileptic Disorders, 18*(1); 58-515.

Bittigau, P., Sifringer, M., Felderhoff-Mueser, U., Ikonomidou, C. (2004) Apoptic neurodegenration in the context of traumatic injury to the developing brain. *Experimental and Toxicologic Pathology*; *56*, 83-89.

Brassen, S., Weber, W., Sommer, T. et al (2006). Hippocampal-prefrontal encoding activation predicts whether words can be successfully recalled or only recognized. *Behavioral Brain Research*, *171*; 271-278.

Brewster, A., Bender, R., Chen, Y., et al (2002). Developmental febrile seizures modulate hippocampal gene expression of hyperpolarization-activated channels in an isoform- and cell-specific manner. *Journal of Neuroscience*, *22*(1); 4591-4599.

Capovilla G, Mastrangelo M, Romeo A, Vigevano F. (2009) Recommendations for the management of febrile seizures: Ad Hoc Task Force of LICE Guidelines Commission.

Epilepsia, 50(l); 2–6

Caesar, P. (1993) Old and new facts about perinatal brain development. *Journal of Child Psychology and Psychiatry, 34*; 101-109

Cendes F, (2004). Febrile seizures and mesial temporal sclerosis. *Neurology, 17*(2), 161-164.

Cendes, F & Sankar R (2011) Vaccinations and febrile seizures. *Epilepsia, 52*; 23–25

Chang, C., Huang, C., Huang, C. (2008) Long-term neuroplasticity effects of febrile seizures in the developing brain. *Chang Gung Med J , 31*; 125–135

Chang YC, Guo NW, Huang CC, Wang ST, Tsai JJ. (2000) Neurocognitive Attention and Behavior Outcome of School-Age Children with a History of Febrile Convulsions: A Population Study. *Epilepsia, 41;* 412-420.

Chang, Y., Guo, N., Wang, S., Huang, C., Tsai , J. (2001) Working memory of school-aged children with a history of febrile convulsions: a population study. *Neurology, 57;* 37-42.

Chen, K., Baram, T., Soltesz, I. (1999). Febrile seizures in the developing brain result in persistent modification oof neuronal excitability in limbic circuits. *Nature Med*, 5(8), 888-894.

Chugani, H., Phelps, M., Mazziotta, C. (1987) Positron emission tomography study of human brain functional development. *Annals of Neurology, 22*; 287-297

Chung, S. (2014). Febrile Seizures. *Korean Journal of Pediatrics, 57*(9), 384-395.

Clarke, A. Tanskanen, M.. Huttunen, M. Clancy, D, Cotter, M. Cannon (2012) Evidence for

shared susceptibility to epilepsy and psychosis: a population-based family study. *Biological Psychiatry, 71*(9); 836–839

Dam, M. (1990) Children with epilepsy: The effect of seizures, syndromes, and etiological factors on cognitive functioning. *Epilepsia, 31*(4); S26-S29.

Dennis, M. (1989) Language and the young damaged brain. *Clinical neuropsychology and brain function: Research, measurement and practice;* 89-123. Washington: American Psychological Association

Donat, J. (1992). The age-dependent epileptic encephalopathies. *Journal of Child Neurology, 7*; 7-21.

Dubé, C.M., et al. (2009) Cognitive dysfunction after experimental febrile seizures. *Exp Neurol, 215*(1): p. 167-77

Dubé C, Vezzani A, Behrens M, et al. (2005) Interleukin-1beta contributes to the generation of experimental febrile seizures. *Ann Neurol, 57*; 152-5

Dulac, O. (2001). Epileptic Encephalopathy. *Epilepsia, 42*(3); 23-26

Eichenbaum, H., (2000) A cortical-hippocampal system for declarative memory. *Nat Rev Neurosci*. *1*(1): p. 41-50.

Ellenberg, J., Nelson, K. (1978) Febrile seizures and later intellectual performance. *Archives of neurology, 35*; 17-21.

Engel Jr. (2001) A proposed diagnostic scheme for people with epileptic seizures and with epilepsy: report of the ILAE task force on classification and terminology. *Epilepsia,*

42(6); 796–803

Engel, J. (2006) Report of the ILAE Classification Core Group. *Epilepsia, 47*; 1558–1568

Fountain, N. (2000) Satus epilepticus: Risk factors and complications. *Epilepsia, 41*(2); S23-S30.

Gibbs, S., Chattopadhyaya, B., Desgent, S., et al (2011). Long-term consequences of a prolonged febrile seizure in a dual pathology model. *Neurobiology of Disease*, *43*, 312-321.

Giza, C., Prins, M., Hovda, D. Herschman, H. Feldman, J. (2002) Genes preferentially induced by depolarization after concussive brain injury: effects of age and injury severity. *Journal of Neurotrauma, 19*(4); 387-402

Hara H, Hara M, Fukuyama Y. (1986) Sustained attention in children with febrile convulsions. *Brain Dev, 8*; 557-8

Harvey, S., Grattan-Smith, D., Desmond, P, et al (1995). Febrile seizures and hippocampal sclerosis: frequent and related findings in intractable temporal lobe epilepsy of childhood. *Pediatric Neurology*, *12*(3), 201-206.

Hauser, A., Annegers, F., Anderson, E., Kurland, T. (1985) The risk of seizure disorders among relatives of children with febrile convulsions. *Neurology, 35*; 1268–1273

Heida, J., Moshé, S., Pittman, Q. (2009). The role of interleukin-1B in febrile seizures. *Brain & Development*, *31*, 388-393.

Hesdorffer DC, Chan S, Tian H, et al. (2008) Are MRI-detected brain abnormalities associated with febrile seizure type? *Epilepsia, 49*; 765–71

Hirtz D. (2002) Cognitive outcome of febrile seizures. In: Baram T, Shinnar S, editors. Febrile seizures. San Diego: Academic Press; 53-62

Hudspeth, W. & Pribram, K. (1990) Stages of brain and cognitive maturation. *Journal of Educational Psychology, 82*; 881-884

International League Against Epilepsy. (1993) Guidelines for epidemiologic studies on epilepsy. *Epilepsia, 34*; 592–6.

Jernigan, T., & Tallal, P. (1990) Late childhood changes in brain morphology observable with MRI. *Developmental Medicine and Child Neurology, 32*; 379-385

Kamal, A., Notenboom, R., Graan, P., Ramakers, G. (2006). Persistent changes in action potential broadening and the slow afterhyperpolarization in rat CA1 pyramidal cells after febrile seizures. *European Journal of Neuroscience*, 23, 2230-2234

Kang, Q., Shen, W., MacDonald, L. (2006) Why does fever trigger febrile seizures? GABA receptor gamma2 subunit mutations associated with idiopathic generalized epilepsies have temperature-dependent trafficking deficiencies. *J Neurosci, 26*; 2590–2597

Kennar, M. (1936) Age and other factor in motor recovery from precentral lesions in monkeys. *American Journal of Physiology, 115*; 138-146

Khan, S. & Baradie, R. (2012). Epileptic Encephalopathies: An overview. *Epilepsy Research & Treatment, 2012*; 8.

Kipp, K., Optiz, B., Becker, M, et al (2012). Neural correlates of recognition memory in children with febrile seizures: evidence form functional magnetic resonance imaging. *Frontiers in Human Neuroscience*, *6*(17), 1-11.

Kipp, K., Mecklinger, A., Becker, M., et al (2010). Infant Febrile Seizures: Changes in declarative memory as revealed by event-related potentials. *Clinical Neurophysiology,*

121, 2007-2016

Kira R, Ishizaki Y, Torisu H (2010) Genetic susceptibility to febrile seizures: case–control association studies. *Brain Dev, 32*; 57–63

Knudsen, F. (1996) Febrile seizures—treatment and outcome. *Brain Dev, 18;* 438-49

Koflen, W., Pehle, K., Konig, S. (1998) Is the long-term outcome of children following febrile convulsions favorable? *Developmental Medicine and Child Neurology*, 40; 667-671

Kupferschmidt, D. & Gordon, J. (2018) The dynamics of disordered dialogue: Prefrontal, hippocampal and thalamic miscommunication underlying working memory deficits in schizophrenia. *Brain and Neuroscience Advances, 2;* 774-783

Kwong, K., Lam, S., Que, T. et al. (2006) Influenza A and febrile seizures in childhood. *Pediatric Neurology, 35*(6); 395-339

Leaffer, E., Hinton, V., Hesdorffer, D. (2013) Longitudinal assessment of skill development in children with first febrile seizure. Epilepsy & Behavior, 28; 83-87

Leung, A. & Robson, W. (2007) Febrile Seizures. *Journal of Pediatric Health Care, 21*(4); 250-255

Leung, A., & Robson, W. (1991) Febrile convulsions: how dangerous are they? *Postgraduate Medicine, 89;* 217- 224

Lewis, D., Shinnar, S., Hesdorffer, D., et al. (2014) Hippocampal sclerosis after febrile status epilepticus: The FEBSTAT study. *Annals of Neurology, 75*(2); 178-185

Li, X., Hou, Y., Ren, Y. et al. (2018). Alterations of theta oscillation in executive control in

temporal lobe epilepsy patients. *Epilepsy Research, 140*; 148-154

Lippé, S., et al. (2009) Altered EEG spectral activity and attentional behavioral deficits following prolonged febrile seizures: a pilot study. *Epileptic Disord, 11*(1); 10-9

Lowenstain, D., Alldredge, B, Pharm, D. (1998) Status epilepticus. *The New England Journal of Medicine,* 338(14); 970-976

Martinos, M., Yoong, M., Patil, S., Chin, R., Neville, B., Scott, R., de Hann, M. (2012) Recognition memory is impaired in children after prolonged febrile seizures. *Brain, 135*; 3153-3164.

Martinos MM, Yoong M, Patil S, Chong WK, Mardari R, Chin RFM, et al. (2013) Early developmental outcomes in children following convulsive status epilepticus: A longitudinal study. *Epilepsia, 54*; 1012-1019

Mastrangelo, M., Midulla, F., Moretti, C. (2014) Actual insights into the clinical management of febrile seizures. *European Journal of Pediatrics, 173*(8), 977-982.

Maytal, J., Shinnar., S. (1990) Febrile Status Epilepticus. *Pediatrics*, *86*, 611-616

Maytal, J., Shinnar, S., Moshé, S., Alvarez, L. (1989) Low morbidity of status epilepticus in children. *Pediatrics, 83*(3); 323-331.

Merkenschlager, A., Todt, H., Pfluger, T et al. (2009). Development of hippocampal sclerosis after a complex febrile seizure. *Eur J Pediatr*, *168*, 487-490.

Michael, S. & Thomas, H. (2003). Epileptic encephalopathy of late childhood: Landau-Kleffner sundrome and the syndrome of continuous spikes and waves during slow-wave sleep. *Journal of Clinical Neurophysiology, 20*(6); 462-472.

Millichap, J., & Millichap, J. (2006) Role of viral infections in the etiology of febrile seizures. *Pediatric Neurology, 35*(3); 165-172.

Moorhty, M., Srinivasan, A., Bhanu, K. (2018) Cognitive impairment in epilepsy. *International Journal of Scientific Research, 7*(4); 2277-8179.

Motamedi, G. & Meador, K. (2003). *Epilepsy & Cognition. Epilpesy & Behavior, 4*(2); 25-38.

Nakahara, S., Adachi, M., Ito, H. et al. (2018). Hippocampal pathophysiology: commonality shared by temporal lobe epilepsy and psychiatric disorders. *Neuroscience Journal, 2018*; 9.

Nazem, A., Hossein, A., Homayoon, S, et al (2012). Neuronal injury and cytogenesis after simple febrile seizures in the hippocampal dentate gyrus. *Childs Nerv Syst*, *28*(11), 1931- 1936.

Norgaard, M., Ehrenstein, V., Nielson, G., Rothman, K., Sorenden, H. (2009) Febrile seizures and cognitive function in young adult life: a prevalence study in Danish conscripts. *Journal Pediatrics, 155*; 404-409.

Notenboom, R., Ramakers, G., Kamal, A. et al (2010). Long-lasting modulation of synaptic plasticity in rat hippocampus after early-life complex febrile seizures. *European Journal of Neuroscience*, *32,* 749-758.

Offringa M, Bossuyt P, Lubsen J, et al. (1994) Risk factors for seizure recurrence in children with febrile seizures: a pooled analysis of individual patient data from five studies. *J Pediatr, 124*; 574-84.

Ozonoff, S. & Jensen, J. (1999). Specific executive function profiles in three neurodevelopmental disorders. *Journal of Autism and Developmental Disorders, 29*(2), 171-177.

Rajab, E., Abdeen, Z., Hassan, Z. et al. (2014) Cognitive performance and convulsive risk after experimentally-induced febrile-seizures in rat. *International Journal of Developmental Neuroscience, 34*; 19-23.

Rao. J. (2013). Brain Development: Neurobehavioral perspectives in development disabilities. *The Clinical Bulleting of the Development Disabilities Division, 24*(1); 1-9.

Reid A, Galic M, Teskey G, Pittman Q (2009) Febrile seizures: current views and investigations. *Can J Neurol Sci, 36*; 679–686

Riley, J.D., et al., (2010) Altered white matter integrity in temporal lobe epilepsy: association with cognitive and clinical profiles. *Epilepsia*, *51*(4); 536-45

Roper, S. (2016) Early life seizures and learning impairment: neither the time nor the place. *EBio Medicine, 7;* 19-20.

Patel , N., Ram. D., Swiderska, N. et al. (2015) Febrile Seizures. *Education Clinical Review, 7;* 22-29.

Patel, A. & Perry, S. (2017) Febrile Seizures: Evaluation and Treatment. *JCom, 24*(7); 325-334.

Pavlidou E (2007) Prospective study of febrile seizures: prognostic factors for subsequent epilepsy. Dissertation, Medical School of Aristotle University of Thessaloniki, Greece

Pavlidou E, Tzitiridou M, Kontopoulos E, Panteliadis C (2008) Which factors determine febrile seizure recurrence? A prospective study. *Brain Dev, 30*; 7–13

Petrides, M., Pandya, D. (2004). Association fiber pathways to the frontal cortex from the superior temporal region in the rhesus monkey. *J. of Comparative Neurology*, *273*(1), 52- 66

Ploghaus, A., Narain, C., Beckmann, C. et al. (2001) Exacerbation of pain by anxiety is associated with activity in a hippocampal network. *Journal of Neuroscience, 21*(24); 9896-9903

Provenzale, J., Barboriak, D., VanLandingham, et al (2008). Hippocampal MRI signal hyperintensity after Febrile Status Epilepticus is predictive of subsequent mesial temporal sclerosis. *AJR*, *190* (4); 976-983

Roy, H., Lippé, S., Lussier, F., Sauerwein, H., Lortie, A., Lacroix, J., Lassonde, M. (2011) Developmental outcome after a single episode of status epilepticus. *Epilepsy & Behavior, 21;* 430-436.

Scantlebury, M.H., et al., (2005) Febrile seizures in the predisposed brain: a new model of temporal lobe epilepsy. *Ann Neurol, 58*(1); 41-9

Scott, R., Surtees, R., Neville, B. (1998) Status epilepticus: pathophysiology, epidemiology, and outcomes. *Arch Dis Child, 79*; 73-77

Scott, R., King, M., Gadian, D. et al (2003). Hippocampal abnormalities after prolonged febrile convulsion: a longitudinal MRI study. *Brain*, *126*, 2551-2557

Saghazadeh, A., Mastrangelo, M., Rezaei, N. (2014) Genetic background of febrile seizures. *Reviews in the Neurosciences, 25*(1)

Shanmugan, S., Wolf, D., Calkins, M. et al. (2016) Common and dissociable mechanisms of executive system dysfunction across psychiatric disorders in youth. *American Journal of Psychiatry, 173*(5); 517-526.

Sheppard, E. & Lippé, S. (2012). Cognitive outcome of status epilepticus in children. *Epilepsy Research & Treatment*; *2012*, 1-8.

Shinnar, S. & Glauser, T. (2002) Febrile Seizure. *Journal of Child Neurology, 17*, s44-s52.

Shinnar, S., Hesdorffer, C., Nordli, R Jr., et al. (2008) Phenomenology of prolonged febrile seizures: results of the FEBSTAT study. *Neurology, 71*; 170–6

Shinnar, S. (2003). Febrile Seizures and Mesial Temporal Sclerosis. *Epilepsy currents*, *3(*4), 115- 118.

Shinner, S., Bello, J., Chan, S., et al. (2012). MRI abnormalities following febrile status epilpeticus in children; The FEBSTAT study. *Neurology, 79*(9), 840-852.

Shinnar, S., Pellock, J., Moshé, S, Maytal, J., O'Dell, C., Driscoll, S., Alemany, M., Newstein, D., DeLorenzo, R. (1997) In whom does status epilepticus occur: age-related differences in children. *Epilepsia, 38*(8), 907-914.

Shinnar, R., Shinnar, S., Hesdorffer, D., et al. (2017). Parental stress, pediatric quality of life, and behavior and baseline and one-year follow-up: Results from the FEBSTAT study. *Epilepsy & Behavior, 69*; 95-99.

Sidman RL, Rakic P. (1973) Neuronal migration, with special reference to developing human brain: a review. *Brain Res, 62*(1); 1–35

Stafstrom, C. (2002) The incidence and prevalence of febrile seizures. In: Baram TZ, Shinnar S, editors. Febrile seizures. San Diego: Academic Press, 1-25

Staudt, M., Schropp, C., Staudt, F. et al. (1993) Myelination of the brain in MRI: a staging system. *Pediatric Radiology, 23*; 169-176

Statz, P., Strauss, E., Hunter, M., Juhn, W. (1994) Re-examination of the crowding hypothesis: Effects of age at onset. *Neuropsychology*; *8*(2); 255-262

Strauss, E., Loring, D., Chelune, G. et al. (1995) Predicting cognitive impairment in epilepsy: Findings from the bozeman epilepsy consortium. *Journal of Clinical and Experimental Neuropsychology, 17*(6); 909-917

Tailby, C., Kowalczyk, M., Jackson, G. (2018). Cognitive impairment in epilepsy: the role of reduced network flexibility. *Annals of Clinical and Translational Neurology, 5*(1); 29-40.

Thebault-Dagher, F., Herba, C., Seguin, J., et al. (2017). Age at first febrile seizure correlated with perinatal maternal emotional symptoms. *Epilepsy Research, 135*; 95-101.

Toth, Z., Yan, X., Haftoglou, S., Ribak, C., Baram, Z. (1998) Seizure- induced neuronal injury: vulnerability to febrile seizures in an immature rat model. *J Neurosci*, *18*; 4285–94.

Trinka, E., Cock, H., Hesdorffer, D., et al. (2015). A definition and classification of status epilepticus - Report of the ILAE Task Force on Classification of Status Epilepticus. *Epilepsia; 56(*10), 1515-1523.

Tsai, M., Hung, K., Tsan, Y., Tao-Hsin, W. (2015) Long-term neurocognitive outcome and auditory event-related potentials after complex febrile seizures in children. *Epilepsy & Behavior, 47*; 55-60.

Van Esch, A., Ramlal, I., Van Steensel-Moll, H., Steyerberg, E., Derksen-Lubsen, G. (1996) Outcome after febrile status epilepticus. Developmental Medicine and Child *Neurology*, 38; 19-24

VanLandingham, K.E., et al., (1998) Magnetic resonance imaging evidence of hippocampal injury after prolonged focal febrile convulsions. *Ann Neurol*, *43*(4); 413-26.

Van Zeij, J., Mullaart, R., Borm, G., Galama, J. (2004) Recurrence of febrile seizure in the respiratory season is associated with Influenza A. *Journal of Pediatrics, 145*(6); 800-805

Verity C, Butler N, Golding J. (1985) Febrile convulsions in a national cohort followed up from birth. Prevalence and recurrence in the first five years of life. *BMJ, 290*; 1307-1310.

Verity, M, Golding, J. (1991) Risk of epilepsy after febrile convulsions: a national conhort study. *Br Med J, 303*; 1373–1376

Verity, M., Greenwood, R., Golding, J. (1998) Long-term intellectual and behavioral outcomes of children with febrile convulsions. *New England Journal of Medicine, 338;* 1723-1728

Vestergaard, M, Pedersen, C, Sidenius, P, Olsen, J, Christensen, J. (2007) The long-term risk of epilepsy after febrile seizures in susceptible groups. *Am J Epidemiol, 165*; 911–918

Vestergaard, M., Pedersen, C, et al (2005) Febrile seizures and risk of schizophrenia. *Schizophrenia Research*, *73*(2); 343– 349

Visser, A., Jaddoe, V., Ghassabian, A., Schenk, J., Verhulst, F., Hofman, A., Tiemeier, H., Moll, H. (2012) Febrile seizures and behavioral and cognitive outcomes in preschool children: the Generation R Study. *Developmental Medicine & Child Neurology,* 1006-1011.

Wall, P. & Messier, C. (2001). The hippocampal formation - orbitomedial prefrontal cortex

circuit in the attentional control of active memory. *Behavioural Brain Research, 127*(1-2); 99-117.

Waruiru, C., & Appleton, R. (2004). Febrile seizures: an update. *Archives of Disease in Childhood, 89,* 751-756.

Wasterlain, C., Fujikawa, D., Penix, L., Sankar, R. (1993) Pathophysiological mechanisms of brain damage from status epilepticus. *Epilepsia, 34*(1); S37-S53

Weiss, E., Masur, D., Shinnar, S., Hesdorffer, et al. (2016) Cognitive functioning one month and one year following febrile status epilepticus. *Epilepsy & Behavior, 64*; 283-288

Wu, W.C., et al., (2005) Hippocampal alterations in children with temporal lobe epilepsy with or without a history of febrile convulsions: evaluations with MR volumetry and proton MR spectroscopy. *AJNR Am J Neuroradiol*. *26*(5); 1270-5

Yamatogi, Y. & Ohtahara, S. (1981). Age-Dependent Epileptic Encephalopathy: A longitudinal study. *Psychiatry and Clinical Neurosciences, 35*(3); 321-332

Yakovlev, P. (1962) Morphological criteria of growth and maturation of the nervous system in man. *Research Publications Association for Research in Nervous and Mental Disease, 39*; 3-46

Yoong, M., Martinos, M., Chin, R. et al. (2013) Hippocampal volume loss following childhood convulsive status epilepticus is not limited to prolonged febrile seizures. *Epilepsia, 54*(12); 2108-2115