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Chapter 5

Febrile Seizures and Their Contribution to Temporal Lobe Epilepsy and Associated Cognitive Problems

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5.1 Introduction: Temporal lobe epilepsy and its antecedents

Spontaneous seizures are the most overt manifestation of epilepsy, a disorder that affects ~1% of the general population [Browne and Holmes, 2008; Hesdorffer *et al.*, 2011a; Zack and Kobau, 2017]. The seizures, and their unpredictability, lead to decreased quality of life in affected individuals, who are often unable to drive and may experience stigmatization from peers in the community. Temporal lobe epilepsy (TLE), a type of epilepsy involving the hippocampal-limbic circuit, is particularly difficult to treat, and one-third of patients with TLE experience seizures that are refractory to anticonvulsant medication [Schmidt and Löscher, 2005]. TLE often arises in

adolescence, leading to decades of decreased quality of life and medical costs.

In addition to the overt burden of the seizures themselves, epileptic seizures are frequently accompanied by problems in memory and executive functions that contribute to poor quality of life [Loiselle *et al.*, 2016]. This is particularly a problem in TLE, because the temporal lobe is comprised of many brain circuits that are required for learning and memory function. These cognitive deficits, including memory and decision-making difficulties, often begin while patients are still in school, further hampering their education and future career potential [Helmstaedter *et al.*, 2003]. In fact, whereas the seizures in TLE have been considered the cause of memory problems, recent studies show that memory deficits often arise either before the onset, or independently of spontaneous seizures [Aikia *et al.*, 2001; Chowdhury *et al.*, 2014; Elger *et al.*, 2004; Hoppe *et al.*, 2007; Weiss *et al.*, 2017]. This suggests that cognitive deficits in chronic epilepsy cannot be exclusively interpreted as long-term effects of the seizures or anticonvulsant drugs. In addition to learning and memory related difficulties, children with epilepsy have significantly higher rates of depression (23%) and anxiety (36%) than their healthy peers, and these disorders can appear prior to or within months of the first epileptic seizure [Jones *et al.*, 2007].

TLE most commonly arises in individuals with a history of long childhood febrile seizures or febrile status epilepticus (FSE) [French *et al.*, 1993; Harvey *et al.*, 1995]. An ongoing study, the FEBSTAT study, has been following 199 children from the onset of FSE. This is the first large-scale prospective research on children that combines early brain imaging, cognitive and medical outcome measures. Results from this groundbreaking study, which started in 2002, have recently begun to emerge. It has confirmed previous findings in animal and human studies that FSE directly provokes hippocampal injury [Lewis *et al.*, 2014; McClelland *et al.*, 2016; Provenzale *et al.*, 2008; Shinnar *et al.*, 2012] and memory impairments [Martinos *et al.*, 2012; Weiss *et al.*, 2017]. Here we discuss the emerging evidence that FSE may contribute to both the seizures and the cognitive problems that are often an intrinsic component of TLE.

5.2 FSE contributes to the development of the seizures that define temporal lobe epilepsy: Support from human and experimental approaches

A subset of individuals with TLE, the most common epilepsy syndrome in adults, have a history of prolonged childhood febrile seizures [Hesdorffer *et al.*, 2011b]. Febrile seizures (FS) are defined as seizures that are associated with a fever without a central nervous system infection or acute electrolyte imbalance in a child without a previous afebrile seizure. Febrile seizures occur in children between six months and five years of age, with the peak incidence at 18 months (AAP Subcommittee on Febrile Seizures, 2008). Febrile seizures are common (affecting 2–5% of the population) and are normally brief and benign — there are no long-term consequences of a single short episode. A subset of FSs are long, lasting >30 minutes, and are categorized as FSE. This type of seizure comprises 25% of all pediatric status epilepticus and is estimated to affect between 25,000–30,000 children annually [Shinnar *et al.*, 1997]. For decades, we have known of a connection between early life FSE and the later development of TLE. In recent years, the FEBSTAT study and additional reports have begun to uncover that FSE may directly cause epilepsy, likely in concert with and in addition to genetic factors. There is an average of an 8–12 year period of network remodeling known as the latent period between FSE and the first epileptic seizure (Berg and Shinnar, 1996; Dubé *et al.*, 2007; Mathern *et al.*, 1995).

Prospective human studies enable us to identify a defining relationship between FSE and the risk of developing TLE or cognitive deficits. Human studies do not allow determination of whether FSE is a causal factor in TLE as clearly, genetic and other factors are contributors [Eckhaus *et al.*, 2013; Hildebrand *et al.*, 2016; Martin *et al.*, 2010a; Nur *et al.*, 2012]. As outlined in Figure 5.1, there are three plausible scenarios: A) FSE is the direct cause of TLE and/or cognitive deficits, and the brain would have developed normally without the febrile seizure; B) FSE develops in an already predisposed brain, but also contributes independently to the development of TLE and/or

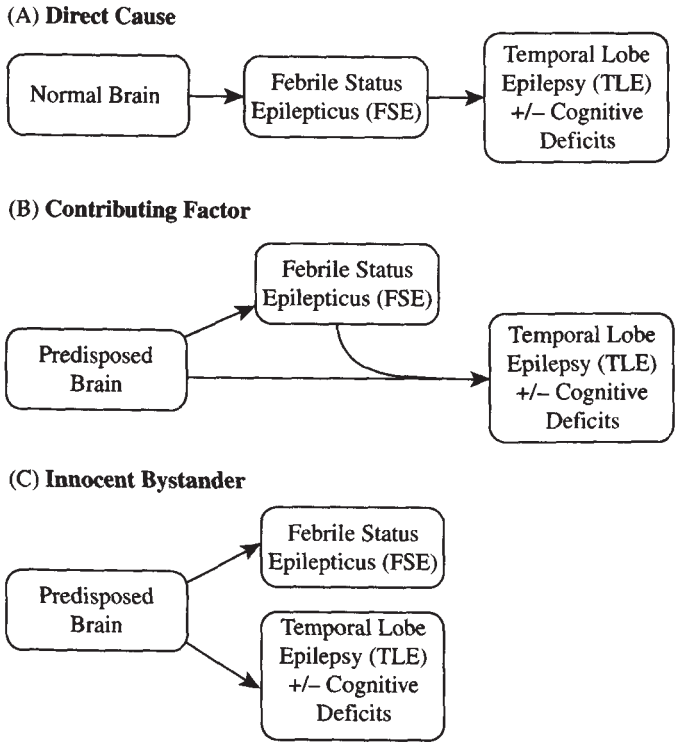

Figure 5.1. Development of febrile status epilepticus and later temporal lobe epilepsy and cognitive deficits.

cognitive deficits; or C) TLE and/or cognitive deficits develop via an independent process from the FSE, and FSE is just an "innocent bystander." We have generated a rodent model of experimental (e)FSE that provides a powerful tool to probe these alternatives.

Specifically, we have employed an age-appropriate model in rats, and found that eFSE directly causes limbic, temporal lobe-like epilepsy [Choy *et al.*, 2014; Dubé *et al.*, 2006, 2010]. The model is based on the hyperthermia that is the most obvious symptom of fever in children. Additionally, in children, the fever is normally caused by inflammation due to an infection, and the same inflammatory mediators are also both involved and required for the invocation of seizures in eFSE [Dubé *et al.*, 2005]. Hyperthermia is induced in rat pups via a regulated stream of warm air for 60 minutes. Heating time is

adjusted to keep their core temperature within the range that invokes febrile seizures as recorded via electroencephalography (EEG), between 38.5–41.0°C [Baram *et al.*, 1997]. Both wild-type and genetically susceptible stains of mice have been used in these experiments, revealing that while genetics increases predisposition to FSE [van Gassen *et al.*, 2008; Martin *et al.*, 2010b], genetic susceptibility is not required for the generation of FSE or the permanent brain changes that FSE can cause [Dubé *et al.*, 2006, 2010; Lemmens *et al.*, 2009]. The age of immature rats (postnatal day 10–11, P10–11) that is used in eFSE reflects the developmental stage when the majority of human FSE occurs [Dubé *et al.*, 2007]. Behavioral seizures in immature rats include the arrest of hyperthermia-induced hyperkinesis followed by facial automatisms. Starting within months after FSE, 30–40% of the rats begin to develop spontaneous limbic seizures (temporal lobe epilepsy), a number similar to the human population [Annegers *et al.*, 1987; Choy *et al.*, 2014; Dubé *et al.*, 2006, 2010; Hesdorffer *et al.*, 2011a]. Therefore, the experimental approach provides strong support for a direct contribution of FSE to the development of TLE rather than TLE being caused by genetics, a supposition supported also by human twin studies [Jackson *et al.*, 1998].

5.3 FSE generates cognitive deficits in a subset of individuals: Support from human and experimental studies

The prevailing dogma in the child neurology literature has been that FSE does not lead to cognitive problems, but instead, memory problems are a result of the brain pathology that also underlies FSE [Chang *et al.*, 2000; Verity *et al.*, 1998]. Over the past decade, compelling information from both human studies [Martinos *et al.*, 2012; Nørgaard *et al.*, 2009; Shinnar *et al.*, 2012] and rodent models [Barry *et al.*, 2016; Dubé *et al.*, 2009; Patterson *et al.*, 2017] has challenged this prevailing dogma. Translational and clinical research has begun to uncover the relationship between TLE and cognitive

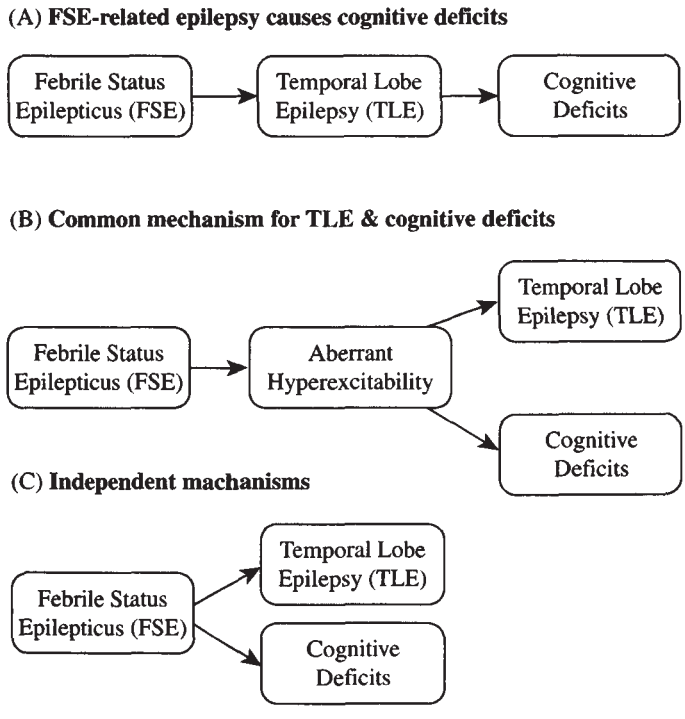

Figure 5.2. Relationship between the origins of temporal lobe epilepsy and cognitive deficits following febrile status epilepticus.

deficits (Figure 5.2) to examine if: A) FSE leads to TLE, which then causes the development of cognitive deficits; B) FSE causes changes within neuronal structure and connections, most likely aberrant hyperexcitability, which then separately (or via overlapping mechanisms) causes TLE and cognitive deficits; or C) TLE and cognitive deficits independently develop via two non-overlapping mechanisms following FSE.

Animal studies have allowed us to separate whether the effect of FSE directly causes cognitive difficulties or if the cognitive difficulties would have developed independent of the febrile seizure, as shown in Figure 5.1C. When rats experience FSE early in life and then are allowed to grow to adulthood, their performance on a variety of cognitive tests including Morris water maze [Dubé *et al.*, 2009], active

avoidance task [Patterson *et al.*, 2017], and novel object location (Curran *et al.*, unpublished) is impaired compared to their littermate controls. By controlling for any genetic or environmental variance that could contribute to performance on cognitive tasks, we can clearly state that FSE directly causes the development of cognitive deficits that continue into adulthood.

Recent work in children has demonstrated that cognitive deficits in children can arise after an epilepsy-inducing insult, but before spontaneous seizures or independently from them [Bender *et al.*, 2013; Elger *et al.*, 2004; Hoppe *et al.*, 2007]. Human studies have revealed that when testing six weeks and one year after FSE, there are deficits in language, motor, and cognitive outcomes, even in children who had no known developmental delays prior to the FSE [Martinos *et al.*, 2013; Weiss *et al.*, 2016]. These findings suggest that FSE-induced memory problems do not depend on a resultant epilepsy that may follow these seizures. Of course, the same limbic/hippocampal networks contribute to memory processes and epilepsy, yet the networks might be affected by independent or partially overlapping processes. Indeed, data from the FEBSTAT study indicate that hippocampal injury following FSE and the memory problems co-exist in the same child [Weiss *et al.*, 2017], lending strong support for the notion that FSE injures the hippocampal circuit and thus induces memory problems. These findings provide major impetus for studying how FSE influences the hippocampal-cortical circuit and how cellular and molecular mechanisms provoke memory deficits.

5.4 Potential mechanisms for FSE-induced seizures and cognitive deficits

5.4.1 *Contribution of inflammation to the consequences of FSE*

Preventing or abrogating the contribution of an acquired insult such as FSE to hyperexcitability and memory problems should be a tractable goal, providing major impetus to study how FSE leads to these

outcomes. Inflammatory processes are excellent candidates for mediating the effects of FSE on both epileptogenesis and memory problems. It has long been known that increased levels of inflammatory cytokines are seen in the brain of both epileptic animals as well as in brain tissue removed from patients with epilepsy [Aronica and Gorter, 2007; Balosso *et al.*, 2013] (also see Chapter 10). Inflammation is a good marker of the abnormal epileptic brain but analyzing differences in tissue after epilepsy has commenced does not allow distinguishing if inflammation is the cause of the spontaneous seizures or an effect of the seizing brain.

As a result of its role in the production of fever, inflammation is inherently linked to the initial febrile seizures [Eskilsson *et al.*, 2014; Heida and Pittman, 2005; Heida *et al.*, 2009; Luheshi *et al.*, 1997; Riazi *et al.*, 2010]. Inflammation not only produces the fever itself, but it also has a direct role in increasing the likelihood of spontaneous seizures from the limbic circuit [Dubé *et al.*, 2007; Patterson *et al.*, 2015; Vezzani *et al.*, 2011].

Not only is inflammation inherent in the febrile basis of FSE, there is an increase in inflammatory markers within the brain following FSE as well as febrile seizures in children. In the experimental model, the onset of the inflammation is fairly rapid, with a measurable increase in messenger RNA (mRNA) as early as one hour after the end of the febrile seizure and nearly completely disappearing by 96 hours post-seizure [Dubé *et al.*, 2010]. This increase is found in the same limbic regions and in the same animals in which an epilepsy-predictive magnetic resonance imaging (MRI) signal is observed [Choy *et al.*, 2014; Patterson *et al.*, 2015]. The inflammatory response consists of a variety of immune markers including cyclooxygenase 2 (COX2), GFAP (an astrocyte activation marker), TNF-α, Interleukin-1β (IL-1β), and Interleukin-1 Receptor 1 (IL-1R1) [Patterson *et al.*, 2015]. Without this increase in inflammation within the brain, particularly IL-1β, the brain is significantly more resistant to febrile seizure, as seen in mice deficient in IL-1β [Dubé *et al.*, 2005]. Thus, inflammation may be both a cause and a reflection of the permanent epileptogenic changes that occur in the brain following FSE.

Inflammation is a particularly enticing target for prevention of epileptogenesis because there are many drugs that are either available clinically or in development that directly interact with the inflammatory cascade. These range from broad anti-inflammatory agents such as dexamethasone (a glucocorticoid receptor agonist), to over-the-counter non-steroidal anti-inflammatory drugs (NSAIDs) including ibuprofen, to drugs that interact specifically with downstream components of the anti-inflammatory cascade, for example TG6-10-1, which blocks prostaglandin E_2 (PGE_2) from binding the EP2 receptor. Many studies in humans and animal models have investigated the use of anti-inflammatory drugs to prevent epileptogenesis with both encouraging [Akula *et al.*, 2008; Gobbo and O'Mara, 2004; Jiang *et al.*, 2015] and negative results [Claycomb *et al.*, 2011; Holtman *et al.*, 2010; Polascheck *et al.*, 2010]. This is likely a result of the fact that while inflammation can cause epileptogenic damage, portions of the inflammatory cascade may be neuroprotective and important for restoring normal neuronal function [Schwartz and Kipnis, 2005].

5.4.2 *Cellular and molecular level changes underlying epilepsy and cognitive problems*

The effects of insults, including long seizures such as FSE, on neurons and brain circuits are highly age dependent. Whereas adult seizures are known to promote neuronal death [Fujikawa, 1996], even prolonged seizures lead to minimal cell death during the early postnatal period [Dubé *et al.*, 2010; Sankar *et al.*, 1998; Toth *et al.*, 1998]. Indeed, the lack of cell death was perennially used as an argument that seizures had little consequence on the developing brain, and that any cognitive impairments observed following long developmental seizures were a result of pre-existing factors [Baram *et al.*, 2011].

Over the past decade, compelling data from both human studies and rodent models [Dubé *et al.*, 2004; Patterson *et al.*, 2015] suggest that functional consequences of early-life insult can arise without cell death. Indeed, whereas the developing brain is more resilient to seizure-induced excitotoxicity [Sullivan *et al.*, 2003], the immaturity of neuronal populations and networks engenders specific vulnerability

of the developing brain [Haut *et al.*, 2004]. There is a widespread consensus, based on diverse approaches in rats and mice, that developing dentate gyrus granule cells (GCs) exhibit maturation-dependent vulnerability to SE: a subpopulation of GCs undergoes structural and functional reorganization following a pro-epileptic insult [Hosford *et al.*, 2016; Kron *et al.*, 2010]. Cells born roughly two weeks before to two weeks after the SE insult either develop hilar basal dendrites (HBD), migrate into the hilus or both, thus contributing to the aberrant circuitry [Goldberg and Coulter, 2013] underlying hyperexcitability and loss of precision in the DG. HBDs are apparent on newborn granule cells, but are normally lost with GC maturation and are targets of both autaptic excitatory synapses as well as excitatory synapses from neighboring GCs [Kron *et al.*, 2010]. This leads to an increase of excitation and increased susceptibility to seizures. We have evidence of retention of immature HBDs in GCs exposed to "SE" in vitro and of abnormal numbers of GCs with this immature feature in adult rats that experienced FSE as pups [Patterson *et al.*, 2017].

Additionally, we discovered that FSE leads to dendritic stunting in hippocampal pyramidal cells [Choy *et al.*, 2014; Patterson *et al.*, 2017] without evidence for cell loss [Dubé *et al.*, 2010; Patterson *et al.*, 2015; Toth *et al.*, 1998]. Other developmental insults such as chronic early-life stress were also found to promote impoverishment of apical dendritic trees and loss of synapses in hippocampal CA1 and CA3 that correlated directly with memory problems [Brunson *et al.*, 2005; Ivy *et al.*, 2010]. Accordingly, interventions that rescued dendrites and synapses ameliorated the memory problems [Ivy *et al.*, 2010]. Because of the close, apparently causal relationship of dendritic and synapse loss and memory problems [Chen *et al.*, 2004; Ivy *et al.*, 2010; Patterson *et al.*, 2017], this structural change provides a reproducible biomarker and target for intervention.

We have now begun to identify neuronal pathways that contribute directly to FSE-induced cognitive impairments, as their blockade rescues cognition. We performed transcriptomic analyses followed by bioinformatics and discovered coordinated transcriptionally-regulated changes in the expression of multiple genes that govern neuronal behavior. Importantly, this pro-epileptogenic transcriptional program

involved Neuron-Restrictive Silencing Factor (NRSF), which is uniquely poised to mediate neuronal plasticity. Originally, NRSF expression was described in non-neuronal tissues where it suppresses neuron-specific genes [Chen *et al.*, 1998; Schoenherr and Anderson, 1995], indicating that neuronal genes carry NRSF-response elements (NRSEs) and are repressed by augmented NRSF levels to prevent expression in non-neuronal tissue [McClelland *et al.*, 2014]. Recently, NRSF expression in mature neurons has been described, where the factor may be crucial for normal function [Ballas and Mandel, 2005; Gao *et al.*, 2011; Singh-Taylor *et al.*, 2017]. NRSF's function is especially crucial in developing neurons, where expression of NRSF-regulated genes contributes to several aspects of maturation, including development of excitatory synapses [Chen *et al.*, 1998; Schoenherr and Anderson, 1995]. This is important, because during the developmental epoch when FSE takes place (infancy and early childhood in humans, P10-11 in the rat [Avishai-Eliner *et al.*, 2002]), many brain neurons are largely mature, but specific neuronal populations including granule cells (GCs) in the dentate gyrus (DG) are still differentiating and maturing [Schlessinger *et al.*, 1975; Thind *et al.*, 2008]. GCs should therefore be more affected by aberrantly increased levels of NRSF.

Seizures may increase NRSF levels and activity [Brennan *et al.*, 2016; Garriga-Canut *et al.*, 2006; McClelland *et al.*, 2011, 2014; Rodenas-Ruano *et al.*, 2012; Roopra *et al.*, 2001]. We found that this was also the case for FSE [Patterson *et al.*, 2017], and then measured the effects of NRSF blockade on cognition in adulthood. Rats that had NRSF binding blocked acutely for two days following FSE performed at the same levels as control rats on the active avoidance task, and significantly better than the rats that had FSE without NRSF blockade. These performance enhancements were already apparent on the second day of training and persisted for at least a month [Patterson *et al.*, 2017].

Acute NRSF blockade not only prevented memory problems, but also rescued the normal maturation of DG-GCs following FSE as measured by the number of abnormal hilar basal dendrites. Together, these facts suggest that gene-sets repressed by NRSF are a

promising candidate mechanism for the FSE–induced abnormal structure and function of the hippocampal-cortical network. Importantly, the number of involved genes is likely to be relatively small; whereas ~600 hippocampal genes are potential targets of NRSF, increased NRSF levels after SE repressed only ~30 target genes in adult hippocampus, governed by the affinity of these genes to NRSF [McClelland *et al.*, 2014].

5.5 Predicting which child with FSE will develop epilepsy and/or cognitive problems

Currently, there is no practical way to predict the epilepsy or cognitive problems that follow FSE. Prediction would enable the development of a way to halt the epileptogenic and cognitive changes before they occur, and then to focus treatment on the children that are at risk. One of the most promising techniques available to track epileptogenic brain changes is MRI. MRI is non-invasive, clinically available, and is a direct measurement of underlying biological structure. It has long been known that there are MRI changes in the following FSE [Dubé *et al.*, 2004; Scott *et al.*, 2003; Shinnar *et al.*, 2012], but these changes have not been able to accurately predict future development of TLE. We described a non-invasive magnetic resonance imaging (MRI) signal that predicts which immature rats exposed to eFSE will develop epilepsy and which will remain unaffected [Choy *et al.*, 2014; Curran *et al.*, 2018]. These MRI scans were taken at a much earlier time point than previous studies, within four hours after eFSE, and reveal a reduced T_2 signal throughout the limbic circuit, and the reduction in the basolateral amygdala (BLA) was strongly predictive of development of epilepsy.

The signal change was initially found on an 11.7T high magnetic field T_2 MRI, but can also be found in a lower-strength 4.7T scanner using a T_2* signal, which can measure changes in deoxyhemoglobin [Chavhan *et al.*, 2009]. The signal reduction likely represents paramagnetic susceptibility effects derived from increasing unsaturated venous deoxyhemoglobin, supported by a strong inverse correlation of deoxyhemoglobin in venous blood with brain T_2 values in a strong

magnetic field (11.7T) [Choy *et al.*, 2014]. Investigation of the mechanisms that underlie the predictive signal changes and continue enhancing their predictive value will hopefully be able to help us inform parents if their child is at increased risk of epilepsy or cognitive deficits and ideally be able to intervene and prevent these.

In the past decade, our knowledge and understanding of how a single long febrile seizure, and specifically febrile status epilepticus, can lead to permanent brain changes has advanced considerably. We have begun to understand the molecular and cellular level changes that begin within minutes of febrile status epilepticus and are changed into adulthood. These changes lead to increased risk of epilepsy and permanent learning and memory deficits, but recent advances move us closer to being able to prevent them.

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